

**A Multicenter Single Arm Phase II Study to Assess the Efficacy of Pembrolizumab Plus  
 Radiotherapy in Metastatic Triple Negative Breast Cancer Patients**

PROTOCOL FACE PAGE FOR  
 MSK THE THERAPEUTIC/DIAGNOSTIC PROTOCOL

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**Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.**

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## List of Abbreviations

Abbreviation or Specialized Term	Definition
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BC	breast cancer
CBC	complete blood count
CEA	carcinogenic embryonic antigen
CMP	complete metabolic panel
CD	cluster of differentiation
CI	confidence interval
CNS	central nervous system
CR	complete response
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte antigen 4
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
EKG	electrocardiogram
ELISA	enzyme-linked immunosorbent assays
EU	European Union
FDA	Food and Drug Administration
FFPE	formalin fixed paraffin embedded
HBV	hepatitis B virus

HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
IEC	Independent Ethics Committee
IFN	interferon
IHC	immunohistochemistry
IMF	Immune Monitoring Facility
IRB	Institutional Review Board
irAE	immune-related adverse event
irRC	immune-related response criteria
IV	intravenous(ly)
LFT	liver function test
MAb	monoclonal antibody
MSK	Memorial Sloan-Kettering Cancer Center
MDSC	Myeloid derived suppressor cell
miRNA	micro ribonucleic acid
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
NIH	National Institute of Health
NK	natural killer
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival

PBMC	peripheral blood mononuclear cell
PD	progressive disease
PD-1	programmed death 1
PD-L1	programmed death ligand 1
PET-CT	positron emission tests- computed tomography
PK	pharmacokinetics
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
Q2W	every 2 weeks
Q3W	every 3 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
RT	Radiation therapy
SAE	serious adverse event
SD	stable disease
TIL	tumor infiltrating lymphocyte
TNBC	triple negative breast cancer
TNF- $\alpha$	tumor necrosis factor alpha
TSH	thyroid-stimulating hormone
ULN	upper limit of normal



## 1.0 PROTOCOL SUMMARY AND/OR SCHEMA

The primary endpoint of the study is to determine the efficacy of pembrolizumab with RT in subjects with triple negative breast cancer (TNBC), adopting a phase II, Simon two-stage, single-arm design. In the first stage, 9 patients will be enrolled. Among them, if no objective tumor responses are observed, then subject enrollment will be terminated. If at least 1 response is observed, then the study will be expanded to enroll another 8 patients for a total of 17 treated subjects. Eligible patients will have metastatic TNBC that is resistant to conventional chemotherapy or have declined conventional therapy.

The primary endpoint is overall response rate in the unirradiated lesion(s), as defined by RECIST v. 1.1. Secondary endpoints are to assess the safety, overall survival and progression free survival by RECIST v 1.1 criteria after treatment with RT + pembrolizumab. An additional secondary endpoint is to assess the overall response rate by immune-related response criteria (irRC). Exploratory endpoints are to characterize the immunologic response and to evaluate the radiologic changes by PET-CT associated with RT+ pembrolizumab.

All subjects will undergo 3000 cGy in 5 fractions of RT over approximately 1 week, to be started within 1-3 days prior to starting Cycle 1 of pembrolizumab. All patients will have at least one locally advanced or metastatic lesion for which palliative RT is considered appropriate standard therapy, and at least one other measurable index lesion that will not undergo RT. Pembrolizumab will be administered via IV infusion at 200 mg every three weeks (Q3W).

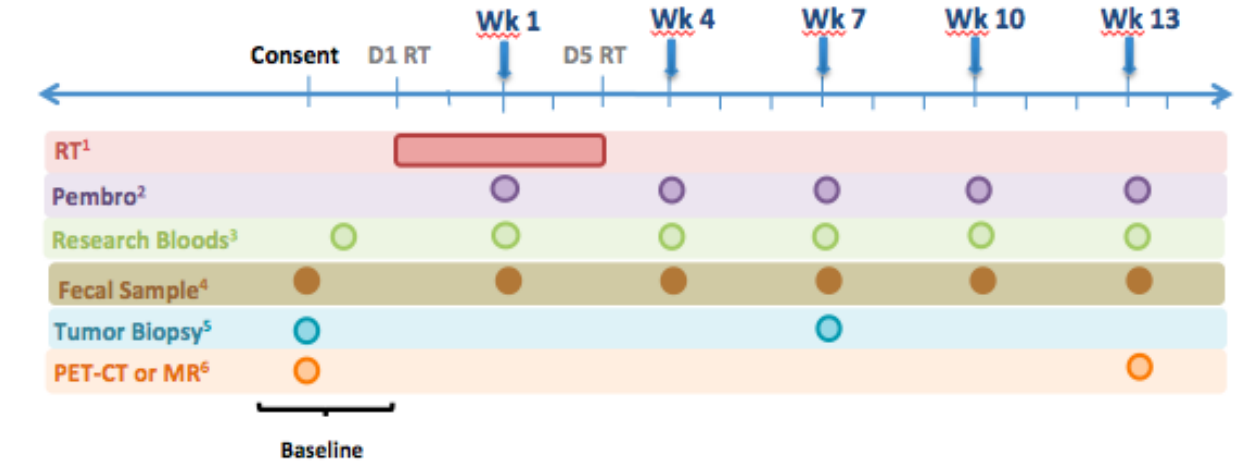
PET-CT or MRI will be performed during screening, at wk 13 ( $\pm 1$  wk) and q9 weeks ( $\pm 1$  wk) thereafter (as per standard care). Tumor measurements and determination of tumor responses will be performed according to RECIST 1.1.

If wk 13 PET-CT or MR demonstrates progression of disease, then pembrolizumab will be discontinued. If wk 13 PET-CT or MR demonstrates complete response, partial response or stable disease, pembrolizumab will be continued q3 weeks until disease progression, up to 24 months. All subjects will be followed up to 2 years or until the study closes.

Mandatory research biopsies will be obtained at baseline and then at week 7 ( $\pm 1$  wk). Peripheral research blood samples will be obtained at baseline, wks 1, 4, 7, 10 and 13 ( $\pm 1$  wk).

It is estimated that up to 17 patients will be enrolled over 2 years.

## Schema:



<sup>1</sup>RT: 3000 cGy x 5 fractions. D1 represents the 1st day of RT (fraction #1).

<sup>2</sup>The first dose of pembrolizumab will be initiated D1-3 of RT. The date of the first dose of pembrolizumab = Wk 1.

<sup>3</sup>Research bloods can be obtained after consent and up to D1 of RT.

<sup>4</sup>Optional fecal samples will be collected from patients within 7 days of each cycle of pembrolizumab.

<sup>5</sup>Baseline imaging must be obtained prior to D1 of RT.

<sup>6</sup>Baseline biopsy may be from archived tissue. If archived tissue is unavailable, it must be obtained prior to D1 of RT. A mandatory research biopsy will be performed at Wk 7 ( $\pm 1$  Wk).

<sup>7</sup>A confirmatory PET-CT or MRI at Wk 19 is only planned for subset of patients in whom Wk 13 scan demonstrates new lesions.

## 2.0 OBJECTIVES AND SCIENTIFIC AIMS

- The primary objective is Overall Response Rate in unirradiated lesion(s) (Complete Response + Partial Response), as defined by RECIST v. 1.1.
- Secondary objectives are:
  - To confirm the safety of pembrolizumab co-administered with RT.
  - To evaluate other disease specific parameters including overall survival and progression free survival by RECIST v 1.1 criteria.
  - To determine overall response rate by immune-related response criteria (irRC).
- Exploratory objectives are:
  - To explore immune-based correlates, as described in detail in Section 12.3.
  - To explore the radiologic changes by PET-CT with pembrolizumab+ RT.

## 3.0 BACKGROUND AND RATIONALE

Triple negative breast cancer (TNBC), defined as estrogen receptor and progesterone receptor levels <1% and HER2 -negative (0-1+ by immunohistochemistry or HER2/CEP17 ratio <2 or HER2 signals/cell <4 by in-situ hybridization [1]), comprises 10-15% of breast cancers. TNBC is associated with rapid growth, early metastasis and unfavorable prognosis compared to other subtypes of breast cancer [2]. Since targeted treatment options such as endocrine therapy and HER2 -directed therapies are unavailable, chemotherapy is the mainstay of treatment. Although both chemotherapy and radiation therapy (RT) are common treatments for palliation and local control in metastatic or recurrent TNBC, there are few effective therapeutic regimens available at this time.

RT has been well described to have numerous immune-modulatory effects. RT-induced tumor cell death increases the supply of tumor-specific antigens, leads to the release of signaling molecules that attract immune cells to the tumor microenvironment and leads to the upregulation of PD-L1 on tumor cells [3,4]. Whether RT combined with PD-L1 blockade can increase the response rate in unirradiated metastases is the subject of this trial.

### **3.1 Rationale for Immune Augmentation in Triple Negative Breast Cancer**

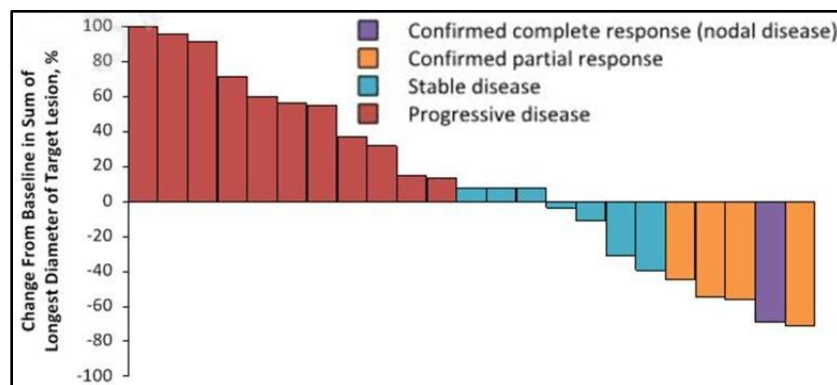
Triple negative breast cancer (TNBC) constitutes 10-15% of breast cancers, but is characterized by disproportionately poor clinical outcomes compared to other subtypes of breast cancer and relatively poor responses to palliative chemotherapy regimens [5]. There is a growing body of evidence indicating that women with TNBC patients are ideally suited for immunotherapy trials. Specifically, dense lymphocytic infiltration has been observed in a significant proportion of TNBCs, indicating an inherent interplay between the tumor and the immune system. Furthermore, numerous adjuvant and neoadjuvant studies have recently shown that the presence of these tumor infiltrating lymphocytes (TILs) confirmed both prognostic and predictive impact [6-9].

Recently published studies suggest that distant metastatic invasion of TNBC may be potentially induced by immune/inflammatory deregulation. Among a set of 45-gene signature that was found to be statistically predictive in distant disease recurrence in TNBC, ten genes are found to be within TGF- $\beta$  signaling pathway, associated with immune suppressed phenotype [10]. In BC patients, either decreased number of effector CD8(+) T cells, or increased number of regulatory T-cells, was associated with adverse tumor characteristics such as lymph node metastasis, higher stage, and Ki-67 immunopositivity [11]. Corroborating these findings, across multiple large adjuvant and neoadjuvant datasets, the quantity of tumor infiltrating lymphocytes in early stage triple negative breast cancers has been associated with improved survival, and increased likelihood of response to chemotherapy [12]. Functional assays demonstrate that

adequate activation of tumor infiltrating lymphocytes (TILs) derived from BC tissue could restore the appropriate antitumor immune responses. This emerging data underscores the potential of a therapeutic strategy that induces immune-mediated anti-tumor responses.

In light of these data, an immunomodulatory agent, pembrolizumab 10mg/kg q2wk, was evaluated in a phase Ib cohort of metastatic TNBC patients [9]. Pembrolizumab is a therapeutic blocking antibody targeting programmed death 1 (PD-1), a surface receptor found on chronically antigen-exposed T-cells associated with downregulation of T-cell cytotoxic activity [13]. In this population (median prior treatments = 2.5), the overall response rate was 19% by RECIST 1.1, with an additional 25.9% with stable disease (figure 3.2.1A). Responses were durable, with the median duration of response not reached (median follow-up 9 mo). The treatment was safe (grade III/IV toxicity: 15.6%). In a similar phase Ib cohort of the anti-program death ligand 1 (PD-L1) antibody, MPDL3470A, an objective response rate of 33% was observed in evaluable TNBC patients [14].

**Figure 3.1.1A Waterfall plot of objective responses to pembrolizumab in TNBC**



### 3.2 Rationale for Immunotherapy plus Radiation Therapy

Radiation therapy (RT) is a standard palliative therapy utilized in patients with metastatic TNBC. RT results in tumor destruction by ionizing radiation in the local region that is specifically targeted within the radiation fields. Therefore, RT is not expected to result in objective systemic benefit. However, RT has been associated with induction of systemic immunity that can be augmented by co-stimulatory blockade with PD-1 leading to potential for tumor shrinkage[15-17].

The phenomenon of tumor destruction by RT leading to shrinking of tumors away from the site of initial treatment has been termed the **abscopal effect**. Albeit rare, when the abscopal effect occurs, the clinical implications can be profound [4].

The rationale of the abscopal effect is that *in situ* tumor destruction releases a large amount of tumor antigens. Antigen-presenting cells, such as dendritic cells, then take up these antigens in the periphery and migrate to lymph nodes where they activate CD4+ and CD8+ T-lymphocytes that recognize these tumor-antigens. Immune augmentation via immune co-stimulatory molecules then permits the ensuing immune response to strengthen and destroy cancer[18,19].

More recently, Dr. Postow from Memorial Sloan-Kettering Cancer Center reported this abscopal effect in a patient who developed a systemic response to localized RT after having had disease progression while receiving CTLA-4 blockade (ipilimumab). Specifically, a right hilar lymph node and spleen metastases, which was not the target of RT, showed regression only after the patient received palliative RT after several months of CTLA-4 blockade. A delayed response to the ipilimumab was considered unlikely [4].

Multiple pre-clinical studies support the combination of RT with anti-PD-1. The combination of radiotherapy and anti-CTLA-4 antibody delayed growth of irradiated tumor, inhibited lung metastases, and improved survival in a 4T1 murine carcinoma model [17]. These findings were confirmed in a 9H10 model, in which combination therapy enhanced primary tumor regression and produced abscopal regression of non-irradiated lesions [16]. Another murine model demonstrated that the combination of radiotherapy and antibodies against CD137 + PD-1 was curative and associated with tumor-antigen specific CD8+ T-cell infiltration [20]. Finally, Deng and colleagues showed that RT enhanced the effect of anti-PDL-1 in the TUBO breast cancer cell line, with reduced TUBO tumor growth after mice were re-challenged in the opposite flank, implying systemic immunity.

The preclinical models and the clinical observation provide compelling rationale to further study RT in combination with immune augmentation by co-stimulatory blockade.

Pembrolizumab is an optimal immunotherapy agent to study, as this agent has recently been FDA-approved for use in metastatic melanoma and is therefore ready to be tested for efficacy in other disease sites and in combination with other treatments. Metastatic TNBC is an ideal target for such a study because 1) there is a lack of effective therapies in heavily pre-treated TNBC and therefore this study represents an opportunity to improve their outcomes 2) TNBC is an immunogenic subtype of breast cancer and 3) RT is commonly indicated for palliation or enhancement of local disease control.

The sequencing and dose/fraction of radiation to optimally harness the proimmunogenic effects of checkpoint inhibitor therapy is unknown. Pre-clinical data suggests that when combined with CTLA-4 antibody antagonists, an oligofractionated regimen was more effective at inducing an abscopal response compared to a single large fraction [4,16,21]. Multiple studies have examined the role of radiation dose and fractionation in generating anti-tumor immune responses[22]. In murine models of RT, several groups have demonstrated enhanced production of circulating IFN-gamma expressing, tumor-specific CD8+ T cells with higher doses of RT (7.5 -15 Gy) delivered focally to tumors.[23] For example, using an MCA38 colorectal cancer model, Dewan et al found that 8 Gy x 3 was most effective in combination with anti-CTLA-4 therapy.[16] However, the best synergy in a 4T1 mammary carcinoma model in combination with CTLA-4 was found with fractionation of 12 Gy x 1 and 12 Gy x 2.[17] Although the preclinical data does not provide a consistent answer as to the best fractionation to use, it can be hypothesized from the preclinical data that higher doses per fraction generate great antigen-release leading to improved anti-tumor immune responses.

We selected 3000 cGy/5 fractions because it is a standard radiation dose/fractionation, which is commonly used in the palliative setting. This dose/fractionation is higher than traditional standard palliative doses, but is generally safe to deliver in virtually all locations throughout the body. This is likely to produce better antigen release. The study permits the first dose of pembrolizumab to be delivered following the initiation of radiation. This would enable enrollment of patients who need to urgently begin palliative radiation.

### **3.3 Rationale for Pembrolizumab Dose Selection/Regimen/Modification**

An open-label Phase I trial (Protocol 001) was conducted to evaluate the safety and clinical activity of single agent MK-3475 (pembrolizumab). The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in-human study of MK-3475 showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified to date. Recent data from other clinical studies with the MK-3475

program has shown that a lower dose of MK-3475 and a less frequent schedule may be sufficient for target engagement and clinical activity.

PK data analysis of MK-3475 administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB).

Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamic data provides scientific rationale for testing a Q2W and Q3W dosing schedule.

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of MK-3475 were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. MK-3475 has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for MK-3475 in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

The rationale for further exploration of 2 mg/kg and comparable doses of pembrolizumab in solid tumors is based on: 1) similar efficacy and safety of pembrolizumab when dosed at either 2 mg/kg or 10 mg/kg Q3W in melanoma patients, 2) the flat exposure-response relationships of pembrolizumab for both efficacy and safety in the dose ranges of 2 mg/kg Q3W to 10 mg/kg Q3W, 3) the lack of effect of tumor burden or indication on distribution behavior of pembrolizumab (as assessed by the population PK model) and 4) the assumption that the dynamics of pembrolizumab target engagement will not vary meaningfully with tumor type.

The choice of the 200 mg Q3W as an appropriate dose for the switch to fixed dosing is based on simulations performed using the population PK model of pembrolizumab showing that the fixed dose of 200 mg every 3 weeks will provide exposures that 1) are optimally consistent with those obtained with the 2 mg/kg dose every 3 weeks, 2) will maintain individual patient exposures in the exposure range established in melanoma

as associated with maximal efficacy response and 3) will maintain individual patients exposure in the exposure range established in melanoma that are well tolerated and safe.

A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage.

## **4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION**

### **4.1 Design**

This will be a Simon two-stage design, phase II study. It will be conducted to determine the efficacy and safety of pembrolizumab plus RT in subjects with metastatic TNBC who are undergoing standard palliative radiation therapy.

### **4.2 Intervention**

All patients will have at least one locally advanced or metastatic lesion for which palliative RT is considered appropriate standard therapy, and at least one other measurable index lesion that will not undergo RT. Only recurrent lesions that are symptomatic and/or requiring palliation will be irradiated. All subjects will begin RT during Cycle 1, within 7 days prior to starting pembrolizumab. Subjects will receive pembrolizumab via IV infusion at 200 mg every three weeks ( $\pm 3$  days), and continue treatment until progression of disease, initiation of alternative cancer therapy, unacceptable toxicity, or other reasons to discontinue treatment occur, up to 24 months. Patients who had a prior response without another reason to discontinue therapy after 24 months will continue clinic visits, routine blood work and PET-CT or MRI every 9 weeks, and may resume treatment for an additional 12 months upon disease progression. Repeat palliative RT will be permitted in select cases for the treatment of isolated, non-target lesions. Patients will be evaluated by physical exam and routine blood tests every three weeks during the study period. PET-CT or MRI will be performed during screening, and then at week 13 ( $\pm 1$  wk) and every 9 weeks ( $\pm 1$  wk) thereafter. Tumor measurements and determination of tumor responses will be performed according to RECIST 1.1.

Subjects may continue to receive pembrolizumab beyond radiographic disease progression in the absence of clinical deterioration, and after discussion with the Principal Investigator.

All subjects will be followed up to 2 years for survival or until the study closes. Exploratory research studies to evaluate the effect of this therapy will be performed in



patients using research blood draws, and tumor biopsy at baseline and week 7 ( $\pm 1$  wk) for research purposes.

#### **4.3 Estimated Duration of Subject Participation**

Subjects may be treated for up to 24 months, with the option to resume treatment for an additional 12 months upon disease progression, unless there is another reason to discontinue treatment. All subjects will be followed for survival for up to 2 years unless the Principal Investigator or Merck decides to end the study.

### **5.0 THERAPEUTIC/DIAGNOSTIC AGENTS**

#### **5.1 Pembrolizumab**

Pembrolizumab will be provided by Merck. Please refer to investigator brochure and MK-3475 Drug Preparation Instructions" manual (Appendix D).

**Table 5.1A Product Descriptions**

<b>Product Name &amp; Potency</b>	<b>Dosage Form</b>
Pembrolizumab 50 mg	Lyophilized Powder for Injection
Pembrolizumab 100 mg/ 4mL	Solution for Injection

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

#### **5.2 Radiotherapy**

Radiotherapy will be performed using external beam ionizing radiation as standard therapy in accordance with institutional standard practice. The dose of radiation will be a standard regimen/fractionation used in palliation: 3000 cGy, delivered in five 600 cGy fractions within 5-7 days.

### **6.0 CRITERIA FOR SUBJECT ELIGIBILITY**

#### **6.1 Subject Inclusion Criteria**

In order to be eligible for participation in this trial, the subject must:

1. Be willing and able to provide written informed consent/assent for the trial.
2. Be female  $\geq 18$  years of age on day of signing informed consent.
3. Histologically or cytologically-confirmed TNBC (defined as ER  $<1\%$ , PR  $<1\%$ , her-2-neu 0-1+ by IHC or FISH-negative or as per MD discretion) at each enrolling institution.
4. Metastatic or locally recurrent TNBC.
5. Subjects who are resistant to conventional chemotherapy or have declined conventional therapy for TNBC. Patients having received any prior line of systemic therapy for inoperable/recurrent or metastatic disease are eligible.
6. At least one tumor for which palliative RT is considered appropriate standard therapy.
7. At least one index lesion that will not undergo RT and which is measurable based on RECIST 1.1.
8. If an archived tumor tissue is unavailable, be willing to provide tissue from a newly obtained core or excisional biopsy of a tumor lesion. Newly-obtained is defined as a specimen obtained up to 6 weeks (42 days) prior to initiation of treatment on Day 1 of RT.
9. Repeat palliative RT will be permitted for the treatment of isolated, non-target lesions.
10. Consent for blood draws for research purposes.
11. Consent for use of available archived tissue for research purposes.
12. Have a performance status of 0 or 1 on the ECOG Performance Scale.
13. Demonstrate adequate organ function as defined in Table 6.1A; all screening labs should be performed within 28 days ( $\pm 7$  days) of treatment initiation, unless otherwise indicated.

**Table 6.1A Adequate Organ Function Laboratory Values**

System	Laboratory Value
<b>Hematological</b>	
Absolute neutrophil count (ANC)	≥1.5 K/mcL
Platelets	≥100 K /mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L without transfusion or EPO dependency (within 7 days of assessment)
<b>Renal</b>	
Serum creatinine <u>OR</u> Measured or calculated <sup>a</sup> creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) <u>OR</u> ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
<b>Hepatic</b>	
Serum total bilirubin	≤ 1.5 X ULN <u>OR</u> Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN <u>OR</u> ≤ 5 X ULN for subjects with liver metastases
Albumin	≥2.5 mg/dL
<b>Coagulation</b>	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants
<sup>a</sup> Creatinine clearance should be calculated per institutional standard.	

14. Female subject of childbearing potential should have a negative pregnancy test or documentation of absence of pregnancy by a gynecologist within 2 weeks of initiating radiation therapy.
15. Female subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication. Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

## 6.2 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

1. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment.
2. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.
3. Has a known history of active TB (Bacillus Tuberculosis)
4. Hypersensitivity to pembrolizumab or any of its excipients.
5. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or who has not recovered (i.e.,  $\geq$  Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.
6. Has had prior chemotherapy or targeted small molecule therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e.,  $\geq$  Grade 1 or at baseline) from adverse events due to a previously administered agent.

Note: Subjects with  $\leq$  Grade 2 neuropathy are an exception to this criterion and may qualify for the study.

7. If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.
8. Has a known additional malignancy that progressed or required treatment in the last 5 years. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.
9. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain parenchymal metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for

at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis, which is excluded regardless of clinical stability.

10. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
11. Has known history of/active, non-infectious pneumonitis requiring treatment with steroids or has history of/active interstitial lung disease.
12. Has an active infection requiring systemic therapy.
13. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
14. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
15. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.
16. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or has participated in another Merck pembrolizumab clinical trial.
17. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
18. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).
19. Has received a live vaccine within 30 days of planned start of study therapy.

Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

## **7.0 RECRUITMENT PLAN**

This study will be available to all patients seen at Memorial Sloan Kettering Cancer Center and Cedars Sinai, who meet the eligibility criteria outlined in section 6.0.

MSK is a large referral center for metastatic TNBC. Drs. Christopher Barker and Ayca Gucalp will facilitate accrual across the Radiation Oncology and Medical Oncology (Breast Medicine) departments, respectively. MSK is equipped with the necessary laboratory infrastructure (i.e. the MSK Immune Monitoring Facility) to conduct the immune monitoring exploratory studies described in section 12.0.

Participants will also be enrolled by Cedars Sinai, a large referral center for breast cancer in southern California.

The investigators take due notice of the NIH policy concerning inclusion of women and minorities in clinical research populations. There will be no limitation to access with regard to race or gender. Patients will be required to read, agree to, and sign an IRB-approved informed consent form prior to registration on this trial. The registration procedure will be conducted as described in section 15.0. Patients will not receive payment for their participation on this study.

Participating site recruitment will be conducted as outlined within the protocol. The participating site that requires a limited waiver must obtain it from its own site IRB/Privacy Board (PB) via a separate protocol addendum or request. It is the responsibility of the MSK staff to confirm that participating data collection site has a limited waiver approval by its local IRB/PB.

## **8.0 PRETREATMENT EVALUATION**

- To be completed within  $28 \pm 7$  days of starting radiation therapy (unless otherwise indicated):
  - PET-CT scan with contrast (diagnostic CT of chest, abdomen and pelvis). If patient is unable to receive CT contrast, or the abdominal/pelvic target lesion is indeterminate on CT scan, then MRI with contrast (abdomen and pelvis) plus CT chest without contrast may be performed. Non-contrast CT CAP may be used if the target lesion(s) do not require contrast for accurate measurements
  - 12-lead Electrocardiogram (EKG)
  - Signed informed consent for study participation
  - History and physical examination including height, weight, vital signs (temperature, pulse rate, respiratory rate, blood pressure, pulse oximetry), performance status (ECOG), and review of pathology and medications.
  - Urine or serum pregnancy test for all women of childbearing potential or documentation of absence of pregnancy by a gynecologist (within two weeks of

starting RT). If the test result is positive related to pregnancy, the patient will not be allowed to participate in this study.

- CBC with differential and platelet count
- Complete metabolic panel (sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, total protein, albumin, bilirubin, alkaline phosphatase, AST, ALT, corrected calcium)
- Magnesium
- Amylase
- Lipase
- LDH
- Phosphorus
- Thyroid function panel (TSH, free & total T3, free T4)
- PT/INR & aPTT
- Serology for HepBsAg, HepBcAb and hepatitis C antibody (negative test prior to screening period is acceptable)
- Tumor markers (CEA, CA 15-3, CA 19-9)
- Research blood samples
- Perform baseline tumor biopsy for diagnostic purposes. Archival biopsy tissue will be used if sufficient tissue is available (at least 1 FFPE-preserved core containing viable tumor), as confirmed by the respective site pathologist. Archival tissue must be obtained within 6 weeks of starting pembrolizumab, with no anti-neoplastic therapies administered between the biopsy and start of pembrolizumab. Archival tissue biopsy specimens can be either from the radiation target or the non-target radiation lesions

## **9.0 TREATMENT/INTERVENTION PLAN**

Subjects will receive pembrolizumab 200 mg as an IV infusion according to the dosing and route described in Table 5.1A. RT begins on D1, prior to dose 1 of Pembrolizumab.

Pembrolizumab will be administered as a 30 minute IV infusion (every effort should be made to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

### **9.1 Monitoring of Dose Administration**

Subjects will be monitored during and after infusion with assessment of vital signs per institutional practice.

In the event of an infusion-related reaction, refer to Appendix C for guidance.

As with any antibody, allergic reactions to dose administration are possible. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis. The study site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit subjects to an intensive care unit if necessary.

## **9.2 Concomitant Medications**

### **9.2.1 Permitted Concomitant Medication**

Investigators may prescribe concomitant medications or treatments (e.g., acetaminophen, diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care except for those medications identified as “excluded” as listed in Section 9.3.2.

### **9.2.2 Excluded Concomitant Medications**

Subjects must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.

The following medications are considered exclusionary during the study. The Principal Investigator must be notified if a subject receives any of these during the study.

- Any investigational anticancer therapy.
- Any concurrent chemotherapy (except as per study), immunotherapy, or biologic therapy.

Note: Concurrent use of bone-directed therapies, such as bisphosphonates or denosumab, are permitted.

- Concurrent use of hormones for non-cancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable.
- Immunosuppressive medications including, but not limited to systemic corticosteroids (>10 mg/day prednisone or equivalent), methotrexate, azathioprine, and tumor necrosis factor alpha (TNF- $\alpha$ ) blockers. Use of immunosuppressive medications for the management of investigational product-related AEs, in subjects with contrast allergies is acceptable. In addition, use of inhaled and intranasal corticosteroids is permitted.

## **9.3 Dose Modifications or Scheduling Delays**



### **9.3.1 Pembrolizumab Dose Modifications**

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment.

Pembrolizumab dose modifications will not be allowed. However, pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 9.3.1A below. See Appendix C (Events of Clinical Interest Guidance Document) for supportive care guidelines, including use of corticosteroids to treat immune related AEs.

**Table 9.3.1A: Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab**

General instructions:				
<ol style="list-style-type: none"> <li>1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.</li> <li>2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to <math>\leq 10</math> mg prednisone or equivalent per day within 12 weeks.</li> <li>3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.</li> </ol>				
Immune-related AEs	Toxicity grade or conditions (CTCAE v4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	<ul style="list-style-type: none"> <li>• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper</li> </ul>	<ul style="list-style-type: none"> <li>• Monitor participants for signs and symptoms of pneumonitis</li> <li>• Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment</li> <li>• Add prophylactic antibiotics for opportunistic infections</li> </ul>
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	<ul style="list-style-type: none"> <li>• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper</li> </ul>	<ul style="list-style-type: none"> <li>• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus).</li> <li>• Participants with <math>\geq</math> Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis.</li> <li>• Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If</li> </ul>
	Grade 4	Permanently discontinue		

				sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	<ul style="list-style-type: none"> <li>Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper</li> </ul>	<ul style="list-style-type: none"> <li>Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)</li> </ul>
	Grade 3 or 4	Permanently discontinue	<ul style="list-style-type: none"> <li>Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper</li> </ul>	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of $\beta$ -cell failure	Withhold	<ul style="list-style-type: none"> <li>Initiate insulin replacement therapy for participants with T1DM</li> <li>Administer anti-hyperglycemic in participants with hyperglycemia</li> </ul>	<ul style="list-style-type: none"> <li>Monitor participants for hyperglycemia or other signs and symptoms of diabetes.</li> </ul>
Hypophysitis	Grade 2	Withhold	<ul style="list-style-type: none"> <li>Administer corticosteroids and initiate hormonal replacements as clinically indicated.</li> </ul>	<ul style="list-style-type: none"> <li>Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)</li> </ul>
	Grade 3 or 4	Withhold or permanently discontinue <sup>1</sup>		
Hyperthyroidism	Grade 2	Continue	<ul style="list-style-type: none"> <li>Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate</li> </ul>	<ul style="list-style-type: none"> <li>Monitor for signs and symptoms of thyroid disorders.</li> </ul>
	Grade 3 or 4	Withhold or permanently discontinue <sup>1</sup>		
Hypothyroidism	Grade 2-4	Continue	<ul style="list-style-type: none"> <li>Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care</li> </ul>	<ul style="list-style-type: none"> <li>Monitor for signs and symptoms of thyroid disorders.</li> </ul>
Nephritis and Renal dysfunction	Grade 2	Withhold	<ul style="list-style-type: none"> <li>Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.</li> </ul>	<ul style="list-style-type: none"> <li>Monitor changes of renal function</li> </ul>
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	<ul style="list-style-type: none"> <li>Based on severity of AE administer</li> </ul>	<ul style="list-style-type: none"> <li>Ensure adequate evaluation to confirm</li> </ul>

	Grade 3 or 4	Permanently dis continue	corticosteroids	etiology and/or exclude other causes
All other immune-related AEs	Intolerable/persistent Grade 2	Withhold	<ul style="list-style-type: none"><li>Based on type and severity of AE administer corticosteroids</li></ul>	<ul style="list-style-type: none"><li>Ensure adequate evaluation to confirm etiology and/or exclude other causes</li></ul>
	Grade 3	Withhold or dis continue based on the type of event. Events that require dis continuation include and not limited to: Guillain-Barré Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently dis continue		
1. Withhold or permanently dis continue pembrolizumab is at the discretion of the investigator or treating physician.				
<b>NOTE:</b>				
For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to $\leq$ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).				

### 9.3.2 Discontinuation of Study Therapy after CR

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least 24 weeks with pembrolizumab and had at least two treatments with pembrolizumab beyond the date when the initial CR was declared. Subjects who then experience radiographic disease progression may be eligible for up to one year of additional treatment with pembrolizumab via the Second Course Phase at the discretion of the investigator if no cancer treatment was administered since the last dose of pembrolizumab, the subject meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial is open. Subjects will resume therapy at the same dose and schedule at the time of initial discontinuation. Additional details are provided in section 9.5.

### 9.3.3 Discontinuation of Study Therapy after PD

Discontinuation of treatment may be considered for subjects who have initial evidence of PD at first re-staging (week 13,  $\pm 1$  wk) and is not clinically stable, or is clinically stable and PD is confirmed 4-6 weeks after the date of first re-staging (weeks 17-19).

#### 9.4 Second Course Phase (Retreatment Period)

Subjects who stop pembrolizumab with SD or better may be eligible for up to one year of additional pembrolizumab therapy if they progress after stopping study treatment. This retreatment is termed the Second Course Phase of this study and is only available if the study remains open and the subject meets the following conditions:

**Either:**

- Stopped initial treatment with pembrolizumab after attaining an investigator - determined confirmed CR according to RECIST 1.1, **and**
- Was treated for at least 24 weeks with pembrolizumab before discontinuing therapy, **and**
- Received at least two treatments with pembrolizumab beyond the date when the initial CR was declared

**Or:**

- Had SD, PR or CR and stopped pembrolizumab treatment after 24 months of study therapy for reasons other than disease progression or lack of safety, **and**
- Experienced an investigator-determined confirmed radiographic disease progression after stopping their initial treatment with pembrolizumab, **and**
- Did not receive any anti-cancer treatment since the last dose of pembrolizumab aside from the assigned chemotherapy backbone, **and**
- Has a performance status of 0 or 1 on the ECOG Performance Scale, **and**
- Demonstrates adequate organ function as detailed in inclusion criteria, **and**
- Does not have a history or current evidence of any condition, therapy, or laboratory abnormality that might interfere with the subject's participation for the full duration of the trial or is not in the best interest of the subject to participate, in the opinion of the treating investigator, **and**
- Meets the following criteria regarding childbearing potential/contraception:
  - Female subject of childbearing potential should have a negative serum or urine pregnancy test within 72 hours prior to receiving retreatment with study medication or have been declared not pregnant by a gynecologist, **and**
  - Female subject of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section 9.5.7). Subjects of child bearing potential are those who have not been surgically sterilized or have been free from menses for > 1 year.

Subjects who restart treatment will be retreated at the same dose and dose interval as when they last received pembrolizumab. Treatment will be administered for up to one additional year. Visit requirements are outlined in the trial flow chart.

## 9.5 Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below and in greater detail in the ECI guidance document. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: if after the evaluation the event is determined not to be related, the investigator is instructed to follow the ECI reporting guidance (Appendix C) but does not need to follow the treatment guidance (as outlined in the ECI guidance document). Refer to Section 9.4 for dose modification.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event. Suggested conditional procedures, as appropriate, can be found in the ECI guidance document (Appendix C).

### Management of Pneumonitis

- For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
- Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

### Management of Diarrhea/Colitis

Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

- All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
- For **Grade 2 diarrhea/colitis** that persists greater than 3 days, administer oral corticosteroids.
- For **Grade 3 or 4 diarrhea/colitis** that persists > 1 week, treat with intravenous steroids followed by high dose oral steroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

**Management of Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or  $\geq$  Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**

- For **T1DM** or **Grade 3-4 Hyperglycemia**
  - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
  - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

**Management of Hypophysitis**

- For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

**Management of Hyperthyroidism or Hypothyroidism:**

Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

- **Grade 2 hyperthyroidism events (and Grade 3-4 hypothyroidism):**
  - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.

- In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyronine, is indicated per standard of care.
- **Grade 3-4 hyperthyroidism**
  - Treat with an initial dose of M corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

### Management of Hepatic toxicities

- For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
  - Treat with M or oral corticosteroids
- For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.
- When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

### Management of Renal Failure or Nephritis

- For **Grade 2** events, treat with corticosteroids.
- For **Grade 3-4** events, treat with systemic corticosteroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

### Management of Infusion Reactions

Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

Table 9.5.3A shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

**Table 9.5.3A: Pembrolizumab Infusion Reaction Treatment Guidelines**

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
<u>Grade 1</u> Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
<u>Grade 2</u> Requires infusion interruption but responds promptly to symptomatic	<b>Stop infusion and monitor symptoms.</b> Additional appropriate medical therapy may include but is not limited to:	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-



NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs.	IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. <b>Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.</b>	3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
<u>Grades 3 or 4</u> Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	<b>Stop Infusion.</b> Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. <b>Subject is permanently discontinued from further trial treatment administration.</b>	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

#### 9.5.4 Management of Nausea/vomiting

Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Subjects should be strongly encouraged to maintain liberal oral fluid intake.

### **9.5.5 Use of anti-infectives**

Subjects with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice.

### **9.5.6 Diet**

Subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.

### **9.5.7 Contraception**

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm. Non-pregnant, non-breast-feeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is  $\geq 45$  years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. The two birth control methods can be either two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Subjects should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study therapy.

The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in section 11.4 - Pregnancies. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

### **9.5.8 Use in Pregnancy**

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor and to Merck without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the

condition of the fetus or newborn to the Sponsor. It is unknown whether pembrolizumab is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breast-feeding are not eligible for enrollment and should be removed from study immediately.

#### **9.6 Subject replacement strategy**

Subjects will be treated on protocol on a modified intention-to-treat analysis, whereby the following subjects will be excluded from analysis and replaced with a newly-enrolled subject:

- Subjects who fail to receive at least part of 1 dose of therapy;
- Subjects who withdraw consent prior to week 13 and/or are lost to follow-up, precluding assessment of safety and efficacy at week 13.

Subjects who clinically progress prior to week 13 and discontinue therapy, but who tolerate therapy up until the point of discontinuation, will not be included in the determination of safety, but will be included as treatment failures in the determination of ORR.

#### **9.7 Clinical Criteria for Early Trial Termination**

Early trial termination will be the result of the criteria specified below:

1. Quality or quantity of data recording is inaccurate or incomplete
2. Poor adherence to protocol and regulatory requirements
3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects
4. Plans to modify or discontinue the development of the study drug

In the event of a Merck decision to no longer supply study drug, ample notification will be provided so that appropriate adjustments to subject treatment can be made.

## 10.0 EVALUATION DURING TREATMENT/INTERVENTION

**Table 10A**

	<b>Screening</b> <b>&lt;28±7 days</b> <sup>3</sup>	<b>Week 1</b> <b>(C1D1)</b>	<b>Week 4</b> <b>(C2D1)</b>	<b>Week 7</b> <b>(C3D1)</b>	<b>Week 10</b> <b>(C4D1)</b>	<b>Week 13</b> <sup>13</sup> <b>(C5D1)</b>	<b>End of</b> <b>study</b> <b>visit</b> <sup>14</sup>
Pembrolizumab <sup>1</sup>		x	x	x	x	x	
Radiation Treatment <sup>2</sup>		x					
Informed consent	x						
Pathology	x						
Medical history	x						
EKG	x						
PET-CT and/or MRI <sup>4</sup>	x					x	
Height and weight	x						
Physical examination	x	x	x	x	x	x	x
Vital signs <sup>5</sup>	x	x	x	x	x	x	x
Performance status	x	x	x	x	x	x	x
Report medications	x	x	x	x	x	x	x
Report side effects			x	x	x	x	x
CBC <sup>6,7</sup>	x	x	x	x	x	x	x
CMP <sup>6,8</sup>	x	x	x	x	x	x	x
Thyroid function panel <sup>6</sup> (TSH, free & total T3 and free T4)	x	x	x	x	x	x	x
CEA, CA 15-3 & CA 19-9 <sup>6</sup>	x	x	x	x	x	x	
Amylase, Lipase, Mg, LDH <sup>6</sup>	x	x	x	x	x	x	x
Phosphorus <sup>6</sup>	x						
PT/INR & aPTT <sup>6</sup>	x						
Hepatitis B and C <sup>6,9</sup>	x						

Pregnancy test <sup>6,10</sup>	x	x	x	x	x	x	
Research bloods <sup>6,11</sup>	x	x	x	x	x	x	
Research tumor biopsy <sup>12</sup>	x			x			
Optional fecal samples for microbiome analysis <sup>15</sup>	x	x	x	x	x	x	

- Each cycle is approximately 3 weeks in duration, corresponds to 1 completed pembrolizumab treatment. Pembrolizumab will begin approximately 1-3 days after start of RT. Subsequent cycles of pembrolizumab will be given q 3 weeks +/- 3 days.
- RT will begin on D1 and consist of 3000 cGy in 5 fractions. RT will be administered prior to dose 1 of pembrolizumab and will be completed within 5-7 days.
- Procedures must be performed within 28 days ( $\pm 7$  days) prior to D1 of RT, unless otherwise indicated.
- PET-CT or MRI will be performed during screening, then at week 13 ( $\pm 1$  wk), then q9 weeks ( $\pm 1$  wk) thereafter. PET-CT includes a separate diagnostic CT of the chest, abdomen and pelvis (CAP) with contrast. If patient is unable to receive CT CAP with contrast or the abdominal/ pelvic target lesion is indeterminate on CT then MRI with contrast (abdomen and pelvis) plus CT without contrast (chest) may be performed. Imaging may be delayed up to 2 weeks if patient is receiving additional RT. Patients who have received prior treatment for brain metastases will receive brain MRIs at week 13 ( $\pm 1$  wk), then q9 weeks ( $\pm 1$  wk) thereafter.
- Vital signs to include temperature, pulse rate, respiratory rate, blood pressure and pulse oximetry.
- Except for screening/baseline blood work, all subsequent blood work will be obtained prior to each dose of pembrolizumab.
- Hematology to include standard complete blood cell (CBC) panel.
- Comprehensive metabolic panel includes: sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, total protein, albumin, bilirubin, alkaline phosphatase, AST, ALT, corrected calcium.
- Serology for HepBs Ag, HepBcAb and hepatitis C antibody (unless previously tested negative).
- Urine or serum pregnancy test or documentation of absence of pregnancy by a gynecologist is required within 2 weeks of starting radiation. Serum is preferred to urine test.
- Blood draws for research purposes performed after obtaining consent but prior to starting RT, then weeks 1, 4, 7, 10 and 13 ( $\pm 3$ d) for all patients. A minimum of 4 CPT tubes of blood will be required at all timepoints.
- Research tumor biopsy will be performed at baseline (only if archived tissue is unavailable) and at wk7 ( $\pm 1$  wk) for all patients. Additionally, up to 20 x 5  $\mu$ m slides (unstained) will be requested on all patients for research purposes.
- Pembrolizumab will continue q3w after the week 13 evaluable timepoint for up to 24 months or until progression of disease, whichever comes first. PET-CT and/or MRI will be obtained q9w ( $\pm 1$  wk) after week 13 until 24 months or POD. No research bloods or fecal samples will be collected after Week 13. However, patients who meet study criteria may remain on-study after Week 13. All clinical and lab assessments will be completed as outlined in table 10A with the exception of the research bloods.
- End of Study visit will occur 2-4 weeks after last dose of pembrolizumab for patients who discontinue the study due to progression of disease or toxicities. PET-CT or MRI to be done only if last imaging was conducted greater than four weeks prior to the date of the End of Study Visit.
- All fecal samples for microbiome analysis are optional and will be directly mailed by the patient in a pre-labeled box addressed to the laboratory for analysis.

### 10.1 Detailed explanation of required evaluations and interventions

Individual trial procedures are described in detail in the Table 10A above. In addition to evaluations/interventions illustrated above, it may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor and/or Merck for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.),

and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

#### **10.1.1 Informed Consent**

Consenting professionals must obtain documented consent from each potential subject prior to participating in a clinical trial.

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB requirements, applicable laws and regulations and Sponsor requirements.

#### **10.1.2 Inclusion/Exclusion Criteria**

All inclusion and exclusion criteria will be reviewed to ensure that the subject qualifies for the trial.

#### **10.1.3 Medical History**

A medical history must be obtained and documented. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the subject has enrolled in this study will be recorded separately and not listed as medical history.

#### **10.1.4 Prior and Concomitant Medications Review**

##### **Prior Medications**

Prior medication use will be reviewed and documented, including any protocol-specified washout requirement, and record prior medication taken by the subject within 28 days before starting the trial. Treatment for the disease for which the subject has enrolled in this study will be recorded separately and not listed as a prior medication.

##### **Concomitant Medications**

Medications will be recorded, if any, taken by the subject during the trial. All medications related to reportable SAEs and ECI should be recorded as defined in Section 11.0.

#### **10.1.5 Disease Details and Treatments**

##### **Disease Details**

Prior and current details regarding disease status must be obtained and documented.

##### **Prior Treatment Details**

All prior cancer treatments including systemic treatments, radiation and surgeries must be reviewed and documented.

#### **10.1.6 Subsequent Anti-Cancer Therapy Status**

All new anti-neoplastic therapy initiated after the last dose of trial treatment must be reviewed and documented. If a subject initiates a new anti-cancer therapy, it is advised that the 30 day Safety Follow-up visit occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the subject will move into survival follow-up.

#### **10.1.7 Adverse Event (AE) Monitoring**

Each subject will be evaluated for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Section 11.2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

For subjects receiving treatment with pembrolizumab all AEs of unknown etiology associated with pembrolizumab exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (termed

immune-related adverse events, or irAEs); see the separate ECI guidance document in Appendix C regarding the identification, evaluation and management of potential irAEs.

Please refer to section 11.2 for detailed information regarding the assessment and recording of AEs.

#### **10.1.8 Full Physical Exam**

A complete physical exam will be performed during the screening period and documented. Clinically significant abnormal findings should be recorded as medical history. A full physical exam should be performed during screening,

#### **10.1.9 Directed Physical Exam**

For cycles that do not require a full physical exam per the Trial Flow Chart a directed physical exam will be performed and documented as clinically indicated prior to trial treatment administration.

#### **10.1.10 Vital Signs**

Vital signs will be taken at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Flow Chart. Vital signs should include temperature, pulse, respiratory rate and blood pressure.

#### **10.1.11 Eastern Cooperative Oncology Group (ECOG) Performance**

ECOG status (see Section 10.0) will be assessed at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.

#### **10.1.12 Laboratory Procedures/Assessments**

After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Blood work must be drawn but not resulted prior to treatment.



### **10.1.13 RESEARCH BLOOD AND BIOPSY SPECIMENS**

#### **10.1.13.1 Research blood**

For all patients, blood specimens will be obtained for research purposes during screening, then at weeks 1, 4, 7, 10, and 13 ( $\pm$  3 days). Specimens should be collected prior to drug administration. Four (4) CPT tubes of blood are to be collected in BD Vacutainer® CPT™ Cell Preparation Tubes with Sodium Heparin. Each tube should contain approximately 10 cc of blood.

For MSK participants, peripheral blood mononuclear cells and plasma will then be isolated per institutional practice in the MSK Immune Monitoring Facility (IMF).

For Cedars-Sinai participants, peripheral blood mononuclear cells and plasma will be isolated and prepared at Cedars-Sinai as per MSK standard operating procedure guidelines (Appendix C). CPT tubes for research blood specimens will be provided by MSK. All specimens will be anonymized, contain the subject's initials, date of birth and date of collection). Participants' full name, date of birth, date of procedure will be shared with MSK. All specimens will be stored in the laboratory of Dr. Stephen Shiao. The blood specimens will be batch-shipped overnight on dry ice to:

Dr. Phillip Wong  
Memorial Sloan Kettering Cancer Center  
409 E. 69<sup>th</sup> St, Z-1513  
New York, NY 10065

Shipments must occur on a Monday, Tuesday or Wednesday in order to be received by the MSK IMF on a Tuesday, Wednesday or Thursday. A requisition for Blood Specimens (Appendix A) must accompany all specimens. Specimens will be tracked by the Medidata Rave database. Dr. Philip Wong, the MSK PI and the Cedars-Sinai Medical Center PI will be notified by email ([wongp@mskcc.org](mailto:wongp@mskcc.org); [barker@mskcc.org](mailto:barker@mskcc.org); [alice.ho@cshs.org](mailto:alice.ho@cshs.org)) when shipments go out and to confirm receipt of shipments. The preferred courier is Federal Express overnight.

**Analysis of all participant's immune markers (described in Section 12.3) will be performed by the MSK IMF (Dr. Philip Wong). Data will be shared throughout the study and at the end of study. MSK secure email or Secure File Transfer System will be utilized to share data across institutions.**

#### **10.1.13.2 Research biopsy**

Pre-treatment tumor tissue will be obtained during screening from archived tumor biopsy tissue performed prior to study enrollment. If archived tissue is unavailable, then a standard of care biopsy of a metastatic lesion will be obtained. An on-treatment research biopsy will be obtained at week 7 ( $\pm$  1 wk), preferably from the same site as

the baseline biopsy and from a non-irradiated lesion. For MSK participants, the lesion(s) that will be biopsied will be at the discretion of the institutional Interventional Radiologist, after discussion with the MSK PI. For Cedars-Sinai Medical Center participants, the lesion(s) that will be biopsied will be at the discretion of the institutional Interventional Radiologist, after discussion with the Cedars-Sinai PI.

Patients will be permitted to continue enrollment and treatment on protocol in the event that insufficient material was obtained from the biopsy. The on-treatment research biopsy will not be required if this is no longer considered appropriate at the time of the planned procedure, for example, if the tumor is no longer accessible or the procedure is deemed to be unsafe. Tumor lesions planned for on-treatment biopsy may be an index lesion if  $\geq 2$  cm in at least one diameter.

If technically feasible, subjects will undergo up to 5 core biopsies. The first three core biopsies will be placed in formalin and processed for FFPE; an additional 2 core biopsies will be immediately frozen in liquid nitrogen and then stored at  $-80^{\circ}\text{C}$  (Appendix B). The minimum core length is 6mm.

For MSK participants, all tissue obtained during biopsy procedures will be sent to Dr. Hannah Wen at MSK Pathology for analysis.

For Cedars-Sinai participants, biopsy specimens will be obtained according to the same instructions as detailed above for MSK participants. All specimens will be anonymized, contain the subject's initials, date of birth and date of collection. Participants' full name, date of birth, date of procedure will be shared with MSK. All specimens will be stored in the laboratory of Dr. Stephen Shiao. For every 5 specimens collected, tissue will then be batch-shipped every overnight at ambient room temperature to:

Dr. Hannah Wen  
Department of Pathology  
MSK  
New York, NY 10065

Shipments must occur on a Monday, Tuesday or Wednesday in order to be received by the MSK IMF on a Tuesday, Wednesday or Thursday. A requisition for Biopsy Specimens (Appendix B) must accompany all submitted specimens. Specimens will be tracked by the Medidata Rave database. Dr. Hannah Wen, the MSK PI and the Cedars-Sinai PI will be notified by email ([weny@mskcc.org](mailto:weny@mskcc.org); [barker@mskcc.org](mailto:barker@mskcc.org); [alice.ho@cshs.org](mailto:alice.ho@cshs.org)) when shipments go out and to confirm receipt of shipments. The preferred courier is Federal Express overnight.

For all participants, analysis of the biopsy specimens will be performed at MSK by Dr. Hannah Wen. Treatment response (treatment effects, tumor cellularity) in on-treatment biopsy and TILs count in the pre- and post- treatment biopsies will be evaluated on the H&E stained sections. Immunohistochemical stains for PD-1, PD-L1, and T-cell markers (CD3, CD4, CD8, FOXP3, CD25) will be performed at the MSK Pathology Core Facility using established protocols with appropriate controls. The immunohistochemical stained sections will be reviewed by Dr. Hannah Wen. PD-1 and PD-L1 expression in tumor cells and in TILs will be scored separately. The expression of T-cell markers will be analyzed in TILs and any changes of expression between baseline and on-treatment biopsies will be noted.

IHC staining for ER, P R and HER2 testing will be performed at the enrolling institution. Data will be shared throughout the study and at the end of study. MSK secure email or Secure File Transfer System will be utilized to share data across institutions.

#### **10.1.14 Tumor Imaging Assessments**

The preferred imaging modality is PET-CT, which will be obtained as per the flow chart schedule. The CT portion of the PET-CT will be a separate dedicated CT scan of the chest, abdomen, and pelvis (CAP) with intravenous (IV) and oral contrast, from which measurements will be made for the primary endpoint of objective response rate using RECIST v. 1.1. If patient is unable to receive IV contrast for the CT, or if the lesion is indeterminate on CT, then MRI with IV contrast (of abdomen and pelvis) could be performed. The CT component of the PET-CT will remain a diagnostic CAP with oral contrast, but no IV contrast.

Patients who have received prior treatment for brain metastases will receive additional brain MRIs at week 13 ( $\pm 1$  wk), then q9 weeks ( $\pm 1$  wk) thereafter, in order to evaluate response in the brain. These assessments will be included in the RECIST measurements.

For Cedars-Sinai participants, all study imaging will be performed at Cedars-Sinai and follow the above guidelines. RECIST reads for the primary endpoint will be performed at Cedars-Sinai. For analysis of the secondary endpoints of immune-related response criteria and PET response criteria, all PET-CT scan imaging will be submitted electronically to MSK co-PI Dr. Lizza Lebron-Zapata for irRC and PRC analyses. Patient name, date of birth, date of procedure and relevant medical history will be shared with MSK. Data will be shared throughout the study and at the end of study. The imaging studies will be sent by Secure File Transfer system to Dr. Lizza Lebron-Zapata at [lebronzl@mskcc.org](mailto:lebronzl@mskcc.org) or by CD-rom mailed to:

Dr. Lizza Lebron-Zapata  
Memorial Sloan-Kettering Cancer Center  
Radiology Department  
500 Westchester Avenue

West Harrison, NY 10604

#### **10.1.15 Withdrawal/Discontinuation**

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events, which are present at the time of discontinuation/withdrawal, should be followed in accordance with the safety requirements outlined in Section 11.2 - Assessing and Recording Adverse Events. Subjects who a) attain a CR or b) complete 24 months of treatment with pembrolizumab may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 9.5. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit (described in Section 10.1.16.1) and then proceed to the Follow-Up Period of the study (described in Section 10.1.16.2).

#### **10.1.16 Visit Requirements**

Visit requirements are described below.

##### **10.1.16.1 Safety Follow-Up Visit**

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded. Subjects who are eligible for retreatment with pembrolizumab may have up to two safety follow-up visits, one after the Treatment Period and one after the Second Course Phase.

##### **10.1.16.2 Follow-up Visits**

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 12 weeks ( $84 \pm 7$  days) by radiologic imaging to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, end of the study or if the subject begins retreatment with pembrolizumab as detailed in Section 9.5. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

Subjects who are eligible to receive retreatment with pembrolizumab according to the criteria in Section 9.5 will move from the follow-up phase to the Second Course Phase when they experience disease progression. Details are provided in Section 9.6.

### 10.1.16.3 Survival Follow-up

Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase and should be contacted by telephone every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

## 11.0 TOXICITIES/SIDE EFFECTS

### 11.1 Summary of toxicities of agents

#### 11.1.1 Pembrolizumab

Pembrolizumab is an FDA-approved agent on formulary for the treatment of metastatic melanoma. It is investigational for use in metastatic TNBC. A comprehensive list of toxicities may be found in Lexicomp and in the investigator's brochure. Principal side effects of pembrolizumab are listed in table 11.1.1A.

**Table 11.1.1A: Principal side effects of pembrolizumab**

Cardiovascular	Peripheral edema
Central Nervous System	Fatigue, headache, chills, insomnia, dizziness, optic neuritis (rare), uveitis (rare)
Endocrine	Hyperglycemia, hyponatremia, hypoalbuminemia, hypertriglyceridemia, hypocalcemia, adrenal insufficiency (rare), hypophysitis (rare)
GI	Nausea, decreased appetite, constipation, diarrhea, vomiting, abdominal pain, pancreatitis (rare), increased serum AST, hepatitis (rare)
Heme	Anemia, hemolytic anemia (rare)
Neurological/Muscular	Arthralgias, limb pain, myalgia, back pain, arthritis (rare), Lambert-Eaton syndrome (rare), myositis (rare), partial epilepsy (rare), rhabdomyolysis (rare),
Respiratory	Cough, dyspnea, upper respiratory tract infection
Miscellaneous	Fever
Dermatologic	Exfoliative dermatitis (rare)
Renal	Interstitial nephritis (rare), nephritis (rare),

#### 11.1.2 Toxicities of Radiation Therapy

Toxicities may occur from radiation treatment. The type and risk of toxicity will depend on the presence of normal tissue structures in close proximity to the target. These normal tissue doses will be constrained by the treatment plan to deliver doses no more

than those recommended in the MSK Department of Radiation Oncology guidelines: (<http://teams.hare/dept/medphys/ebtp/Public%20Documents/Forms/Public%20View.aspx>). These guidelines will be shared with and followed by Cedars-Sinai.

The estimated risks of each type of toxicity are noted below, and include:

1. Grade 2-3 skin (erythema, dry or moist desquamation, patchy ulceration) - 10%
2. Grade 1-2 non-debilitating fatigue- 30%
3. Any grade brachial plexopathy- 5-7%
4. Grade 3 bowel (bowel perforation, obstruction or hemorrhage) - 2-5%
5. Grade 2-4 peripheral nerve (neuropathy or severe neuropathic pain unresponsive to medications)-2-5%
6. Grade 2-4 bladder (hemorrhagic cystitis, chronic cystitis manifesting in frequency and urgency) - 2-5%
7. Grade 2-4 rectum (injury including ulceration or perforation)-2-5%
8. Grade 2-4 osteonecrosis or bone fracture-5-10%

## **11.2 Assessing and Recording Adverse Events**

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Merck's product, is also an adverse event.

Merck product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by Merck for human use.

Adverse events may occur during the course of the use of Merck product in clinical trials or within the follow-up period specified by the protocol, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Adverse events may also occur in screened subjects during any pre-allocation baseline period as a result of a protocol-specified intervention, including washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Progression of the cancer under study is not considered an adverse event unless it is considered to be drug related by the investigator.

All adverse events will be recorded from the time the consent form is signed through 30 days following cessation of treatment and at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 11.2.

### **11.3 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor and to Merck**

For purposes of this trial, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater ( $\geq 5$  times the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab. Appropriate supportive treatment should be provided if clinically indicated. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an adverse event(s) is associated with ("results from") the overdose of a Merck product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Merck's product meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor and within 2 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

### **11.4 Reporting of Pregnancy and Lactation to the Sponsor and to Merck**

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. All subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be

reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

## **11.5 Immediate Reporting of Adverse Events to the Sponsor and to Merck**

### **11.5.1 Serious Adverse Events**

A serious adverse event is any adverse event occurring at any dose or during any use of Merck's product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose;
- Is another important medical event

Refer to Table 11.6-1 for additional details regarding each of the above criteria.

Progression of the cancer under study is not considered an adverse event unless it results in hospitalization or death.

Any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject from the time the consent is signed through 90 days following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to Merck product, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety.

Non-serious Events of Clinical Interest will be forwarded to Merck Global Safety and will be handled in the same manner as SAEs.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to Merck product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor and to Merck.

**SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-993-1220**



A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally investigators will submit a copy of these reports to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215 993-1220) at the time of submission to FDA.

All subjects with serious adverse events must be followed up for outcome.

### **11.5.2 Events of Clinical Interest**

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event case report forms/worksheets and reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220) Events of clinical interest for this trial include:

1. An overdose of Merck product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.
2. An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.\*

\*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

### **11.5.3 Additional adverse events**

A separate guidance document has been provided entitled "Event of Clinical Interest Guidance Document" (previously entitled, "Event of Clinical Interest and Immune-Related Adverse Event Guidance Document"). This document can be found in Appendix C and provides guidance regarding identification, evaluation and management of ECIs and irAEs.

ECIs (both non-serious and serious adverse events) identified in this guidance document from the date of first dose through 90 days following cessation of treatment,

or 30 days after the initiation of a new anticancer therapy, whichever is earlier, need to be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220), regardless of attribution to study treatment, consistent with standard SAE reporting guidelines.

Subjects should be assessed for possible ECI prior to each dose. Lab results should be evaluated and subjects should be asked for signs and symptoms suggestive of an immune-related event. Subjects who develop an ECI thought to be immune-related should have additional testing to rule out other etiologic causes. If lab results or symptoms indicate a possible immune-related ECI, then additional testing should be performed to rule out other etiologic causes. If no other cause is found, then it is assumed to be immune-related.

### **11.6 Evaluating Adverse Events**

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

**Table 11.6A: Instructions of how an investigator should evaluate all adverse events**

<b>V4.0 CTCAE Grading</b>	<b>Grade 1</b>	<b>Mild</b> ; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
	<b>Grade 2</b>	<b>Moderate</b> ; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
	<b>Grade 3</b>	<b>Severe or medically significant but not immediately life-threatening</b> ; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
	<b>Grade 4</b>	<b>Life-threatening consequences</b> ; urgent intervention indicated.
	<b>Grade 5</b>	<b>Death related to AE</b>
<b>Seriousness</b>	<p>A serious adverse event is any adverse event occurring at any dose or during any use of Merck product that:</p> <p>†<b>Results in death</b>; or</p> <p>†<b>Is life threatening</b>; or places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or</p> <p>†<b>Results in a persistent or significant disability/incapacity</b> (substantial disruption of one's ability to conduct normal life functions); or</p> <p>†<b>Results in or prolongs an existing inpatient hospitalization</b> (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse event.); or</p> <p>†<b>Is a congenital anomaly/birth defect</b> (in offspring of subject taking the product regardless of time to diagnosis); or</p> <p><b>Is a new cancer</b>; (that is not a condition of the study) or</p> <p><b>Is an overdose</b> (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.</p> <p><b>Other important medical events</b> that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).</p>	
<b>Duration</b>	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
<b>Action taken</b>	Did the adverse event cause the Merck product to be discontinued?	
<b>Relationship to test drug</b>	<p>Did the Merck product cause the adverse event? The determination of the likelihood that the Merck product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information.</p> <p><b>The following components are to be used to assess the relationship between the Merck product and the AE</b>; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Merck product caused the adverse event (AE):</p>	
	<b>Exposure</b>	Is there evidence that the subject was actually exposed to the Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	<b>Time Course</b>	<p>Did the AE follow in a reasonable temporal sequence from administration of the Merck product?</p> <p>Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?</p>
	<b>Likely Cause</b>	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors
<b>Relationship</b>	<b>The following components are to be used to assess the relationship between the test drug and the AE: (continue d)</b>	

to Merck product (continue d)	<b>De challenge</b>	Was the Merck product discontinued or dose/exposure/frequency reduced? If yes, did the A E resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the A E resulted in death or permanent disability; (2) the A E resolved/improved despite continuation of the Merck product; or (3) the trial is a single-dose drug trial); or (4) Merck product(s) is/are only used one time.)
	<b>Re challenge</b>	Was the subject re-exposed to the Merck product in this study? If yes, did the A E recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial A E resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Merck product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE MERCK PRODUCT, OR IF REEXPOSURE TO THE MERCK PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE U.S. CLINICAL MONITOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	<b>Consistency with Trial Treatment Profile</b>	Is the clinical/pathological presentation of the A E consistent with previous knowledge regarding the Merck product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
<b>Record one of the following</b>	<b>Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Merck product relationship).</b>	
<b>Yes, there is a reasonable possibility of Merck product relationship.</b>	There is evidence of exposure to the Merck product. The temporal sequence of the A E onset relative to the administration of the Merck product is reasonable. The A E is more likely explained by the Merck product than by another cause.	
<b>No, there is not a reasonable possibility Merck product relationship</b>	Subject did not receive the Merck product OR temporal sequence of the A E onset relative to administration of the Merck product is not reasonable OR there is another obvious cause of the A E. (Also entered for a subject with overdose without an associated A E.)	

## 11.7 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations.

## 12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

### 12.1. Evaluation of Primary Endpoint

The primary endpoint of the pilot phase is to Overall Response Rate in unirradiated lesion(s) (Complete Response + Partial Response), as defined by RECIST v. 1.1. The definitions of CR and PR are specifically described in Section 12.1.1.

#### 12.1.1 Response Assessments

For the purposes of this study, patients will be evaluated for response at Week 13 ( $\pm 1$  wk), then every 3 cycles (approximately 9 weeks,  $\pm 1$  wk), or as clinically indicated if interim toxicity occurs mandating cancer staging re-assessment. RECIST v. 1.1 criteria will be used.

#### CT scan with contrast of the chest, abdomen, and pelvis

- CT scans should be performed with contiguous cuts in slice thickness of 5 mm or less. Spiral CT should be performed using a 5-mm contiguous reconstruction algorithm.

#### MRI scans

- MRI of the abdomen and pelvis is acceptable for measurement of lesions provided that the same anatomical plane is used for serial assessments. If possible, the same imaging device should be used for serial evaluations. In case of MRI, measurements will be preferably performed in the axial (transverse) plane on contrast-enhanced T1-weighted images. However, there are no specific sequence recommendations.
- Patients who have received prior treatment for brain metastases will also receive brain MRIs at week 13 ( $\pm 1$  wk), then q9 weeks ( $\pm 1$  wk) thereafter, in order to evaluate response in the brain. These assessments will be included in the RECIST measurements.

#### Measurability of Tumor Lesions

Tumor lesions will be categorized as follows:

- **Measurable Lesions** - Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10 mm)
- 10 mm caliper measurement by clinical exam (when superficial)
- Malignant lymph nodes are considered pathologically enlarged and measurable, a lymph node must be  $\geq 15$  mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).
- **Nonmeasurable Lesions** - Nonmeasurable lesions are defined as all other lesions (or sites of disease), including small lesions (longest diameter  $< 10$  mm or pathological lymph nodes with  $\geq 10$  to  $< 15$  mm short axis). Lesions considered truly nonmeasurable include the following: leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.
- **Target Lesions** - All lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.
- **Non-target Lesions** - It is possible to record multiple nontarget lesions involving the same organ as a single item on the case record form (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases")

## **Response Criteria**

### **Evaluation of Target Lesions**

- **Complete Response** - Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to  $< 10$  mm (the sum may not be "0" if there are target nodes).
- **Partial Response** - At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
- **Progressive Disease** - At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression.)
- **Stable Disease** - Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.

## Evaluation of Non-target Lesions

- **Complete Response** - Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).
- **Non-complete response/Non-progressive disease (Partial Response/Stable Disease)** - Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- **Progressive Disease** - Unequivocal progression of existing non-target lesions will be defined as the overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. In the absence of measurable disease, change in non-measurable disease comparable in magnitude to the increase that would be required to declare PD for measurable disease. Examples include an increase in a pleural effusion from „trace“ to „large,“ an increase in lymphangitic disease from localized to widespread.

## Appearance of New Lesions

The appearance of new lesions is considered PD according to RECIST v 1.1 guidelines. Considering the unique response kinetics that have been observed with immunotherapy, new lesions may not represent true disease progression (Wolchok, Hoos et al.2009) Subjects initially assessed as PD by modified RECIST v 1.1 criteria, in the absence of significant clinical deterioration warranting discontinuation of study treatment will continue treatment and receive a confirmatory scan at least 4 weeks later. The following criteria will be used to determine if study treatment will be continued:

- If the tumor burden at the confirmatory scan is >20% larger than the tumor burden at the initial PD scan, the subject will be considered to have confirmed PD and will be discontinued from study treatment.
- If the tumor burden at the confirmatory scan is within 20% of the tumor burden at the initial PD scan, the subject will be considered to have SD and will continue treatment until the next scheduled scan 3 months after the initial PD. Any subsequent scheduled tumor assessment visit showing that the tumor burden is >20% larger than the tumor burden at the initial PD scan will be considered as confirmed PD, and the subject will be discontinued from study treatment.
- In subjects with new lesions in the setting of overall response, the decision to continue treatment will be discussed on a case by case basis between the PI and study monitor.

- It is important to maintain the schedule of assessments every 3 months and subjects having confirmatory scans for PD must return for the next scheduled visit per protocol.

## Evaluation of Overall Response

Table 12.0 provides overall responses for all possible combinations of tumor responses in target and non-target lesions with or without the appearance of new lesions.

Table 12.0 Evaluation of Overall Response

Target Lesions	Non-target Lesions	New Lesions	Overall Response
Complete response	Complete response	No	Complete response
Complete response	Not evaluable	No	Partial response
Complete response	Non-complete response / non-progressive disease	No	Partial response
Partial response	Non-progressive disease and not evaluable <sup>a</sup>	No	Partial response
Stable disease	Non-progressive disease and not evaluable <sup>a</sup>	No	Stable disease
Not all evaluated	Non-progressive disease	No	Not evaluable
Progressive disease	Any	Yes/No	Progressive disease
Any	Progressive disease	Yes/No	Progressive disease
Any	Any	Yes	Progressive disease

<sup>a</sup> Not evaluable is defined as either when no or only a subset of lesion measurements are made at an assessment.

## 12.2 Evaluation of Secondary and Exploratory Endpoints

### 12.2.1 Secondary Endpoint: Evaluation by immune-related response criteria (irRC)



Because irRECIST not yet been validated in breast cancer, we propose assessing disease control with irRC as a secondary objective. We will assess disease control at 13 weeks using immune-related response criteria (irRC) (Wolchok, Hoos et al. 2009). irRC involves assessment of non-targeted, non-irradiated lesions. Response is defined as irCR, irPR or irSD over a period of at least 4 weeks. Imaging before the week 13 time point will not be specified, to account for the possibility that a subset of patients will experience an immune-related response, by which response are preceded by radiographic progression, related to delayed response kinetics and/or T-cell tumoral infiltration.

### **12.2.2 Exploratory Endpoint: Evaluation by PET Response Criteria (PRC)**

In subjects receiving PET-CT, radiographic response by PET will be compared to standard assessment with CT CAP. This comparison will help evaluate whether metabolic uptake might be useful in distinguishing clinical response to immunotherapy in breast cancer patients, who are frequently evaluated off-protocol with PET/CT.

PET-CT is commonly used as a standard-of-care modality for evaluating response to palliative therapy in metastatic breast cancer. However, on study, response to treatments is often measured anatomically using the RECIST v 1.1 guidelines. However, there are limitations in using anatomic response criteria alone, particularly when evaluating bone metastases without an extraosseous component, which is common in breast cancer patients. Furthermore, while RECIST criteria may be appropriate for evaluating response to conventional cytotoxic therapies, they may not be ideal for evaluating response in the setting of dynamic infiltration with immunotherapy.

“PERCIST” (PET Response Criteria in Solid Tumors), is a commonly proposed method for measuring treatment response based on metabolic response criteria with PET [69]. A limitation of PERCIST is that it only takes into account the single hottest lesion and it relies upon SUV peak measurements, which are not easily reproducible in lesions with low FDG-avidity, as are often found in breast cancer. Since there are no standardized methods for quantifying FDG-tracer avidity in individual tumor lesions, we will use a modification of PERCIST criteria called “PET Response Criteria” (PRC) that is currently being utilized in other cancer protocols at MSK requiring metabolic assessment. In brief, the SUVmax of tumor(s) will be measured and recorded. In order to be consistent with the definition of overall response as defined in the primary endpoint, only non-targeted, non-irradiated tumor(s) will be assessed by PRC. On subsequent studies, the same target lesion will be measured and recorded. Lesions where SUVmax is no greater than background will be recorded as zero.

According to PRC, response or progression will be graded as follows:

**CR: All lesions no greater than background SUVmax**

**PR: SUVmax decreased by  $\geq 30\%$  greater than background**

**SD: Lesions that do not fit criteria for response or progression**

**PD: SUM SUVmax increased by  $\geq 30\%$  or development of a new lesion within the irradiated field**

We anticipate that the most common discrepancy between PRC and RECIST v 1.1 will be when there is a CR on PRC, but PR on RECIST v 1.1. In these cases, RECIST v 1.1 (and not PRC) will be utilized for response assessment. RECIST measurements will be done on the dedicated CT portion of the PET/CT.

### **12.3 Correlative Studies**

Changes in immunologic biomarkers may be evaluated for associations with overall response rate and safety (adverse event) data. Core biopsies may be used for correlative studies such as IHC, tumor mutation analysis, proteomic analysis, and immunodiversity. PDL-1 immunohistochemistry will be done by a Merck designated laboratory. Other correlative study assessments will be done at MSK.

#### **12.3.1 Whole Blood**

Flow cytometry will be performed on baseline and on-treatment to assess baseline and changes in composition/activation status of lymphocyte subsets present in peripheral blood mononuclear cell preparations (PBMCs). Assays may include evaluation of frequencies of CD8+ and CD4+ T-cell subsets (activated/ effector/ regulatory) and their expression of activation, exhaustion, and proliferative markers such as ICOS, Ki-67, PD-1, CTLA-4, LAG-3 and TIM-3. Additional analysis of T cell function in select samples via analysis of production of intracellular cytokines such as IFN-gamma upon activation may be included. NK cell populations may be monitored in a similar fashion with a focus on characterizing subsets defined by the expression of activation markers (e.g. NKG2D; IL-21R) and/or by markers that are associated with the potential of NK cells to lyse target cells (e.g., CD107a, granzyme, perforin). Additional flow cytometry-based assays will focus on defining and monitoring the abundance of myeloid-derived suppressor cells (MDSCs), a cell type which appears to negatively impact anti-tumor activity and which has been shown to promote immune escape by limiting activated CD8 T-cell infiltration into the tumor microenvironment [25]. Immune cells may be evaluated using HLA-A2-restricted tetramer assays to detect and quantify the presence of T cells directed against specific antigens that are anticipated to be presented to the immune system during study treatment. Detecting on-treatment increases in these T cell populations may be considered evidence of adaptive immune responses in TNBC.

#### **12.3.2 Plasma**

To understand the prevalence of circulating proteins and the impact they may have on the clinical activity and/or safety of pembrolizumab treatment, the protein concentrations of a panel of cytokines, chemokines, and other relevant immunomodulatory, soluble factors may

be investigated by ELISA and/or other relevant multiplex-based protein assay methods. Examples of analyses to be assessed may include but are not limited to factors induced by IFN $\gamma$  signaling (e.g., T cell chemoattractants CXCL9; CXCL10) and other factors generally involved in inflammatory processes. Plasma may be used also to assess the presence and/or concentration of anti-tumor antibodies using a multiplex platform such as Invitrogen's ProtoArray platform(c). Levels of sPD-L1 in peripheral blood may also be assessed.

### **12.3.3 Tumor Tissue**

The presence of TILs within tumors in response to pembrolizumab treatment will be evaluated baseline and on-treatment biopsies. Archived tissue (up to 20 x 5  $\mu$ m unstained slides) and biopsy tissue may be analyzed using immunohistochemistry for PD-L1 expression and other immune-related genes, and gene expression (Nanostring and/or RT-QPCR) research platforms. Laser Capture Microdissection may be utilized to enrich specific regions of tumor material for use in similar or additional downstream applications, which may include in-situ hybridization, flow cytometry, ELISA, targeted sequencing using MSK-IMPACT platform, and/or assessment of miRNA. MSK IMPACT testing will be done on tumor tissue from Cedars-Sinai patients, if possible. At MSK, patients will sign MSK IRB#12-245 to have MSK IMPACT testing. At Cedars-Sinai, patients either sign similar genetic profiling institutional protocols or information about the genetic profiling will be placed in the study consent form.

In all cases, the goal may be to determine the abundance of a battery of immunoregulatory genes or proteins associated with cancer cells and/or cancer-interacting lymphocytes derived from biopsied material. Other biomarkers may be evaluated as determined by additional data. Remaining specimens may be stored for future studies related to TNBC immunity.

#### **12.3.3.1 MSK IMPACT Testing**

The consent indicates that samples and genetic information collected may be shared with other qualified researchers and placed in online databases. An example of an online database is the NIH dbGAP database, which is monitored by the National Institutes of Health, and maybe made accessible to investigators approved by the U.S. government. Such information will not include identifying information such as name. It is also stated in the Research Authorization that research data (e.g. genomic sequence) may be shared with regulators. The requirements for submission of genotype/phenotype data into the NIH dbGAP or any other public database will be followed as per the IRB SOP for Genomic Data Sharing.

In the course of this research it is possible that some patients whose tumors are analyzed through investigational "next-generation" profiling in a research (non-CLIA) environment will be found to have somatic or germline mutations in genes that are known to be associated with an increased risk of cancer or other diseases. It will be stated in the consent that the participants will not receive any specific results from research tests. The consent will tell

participants that if they wish to have genetic testing done for personal reasons than they should make an appointment with the MSK Clinical Genetics Service or Clinical Genetics Service at their site.

If in the course of this research a research finding is obtained that, in the opinion of the investigator, may be critical to the preventive care of the participant or their family, the investigator can communicate that finding to the MSK IRB Genomic Advisory Panel (GAP). The finding will be reviewed by the GAP to determine whether the incidental finding should be discussed with the participant. For MSK patients, in the event that the GAP determines that the finding should be discussed with the participant, and the participant has consented to be re-contacted, then the treating/consenting physician shall be contacted by the panel and asked to refer the participant to the Clinical Genetics Service for further discussion of the research finding.

The following information must be provided to GAP for review:

- Participant Name/MRN #
- Type of Biospecimen (tissue, blood, saliva)
- Incidental Finding
- Collection Protocol #
- Contact: [ocrgapirb@mskcc.org](mailto:ocrgapirb@mskcc.org)

For non-MSK patients being treated at one of the participating institutions, in the event the GAP determines that the finding should be discussed with the participant, and the participant has consented to be re-contacted, the findings will be returned to the Site Principal Investigator. Site policies on returning these research findings to the patient should be followed.

[We anticipate that other research assays may be incorporated into this protocol as technology evolves.](#)

#### **12.3.4 Optional Fecal Samples for Microbiome Analysis**

Many factors have been shown to regulate the anti-tumor immune response and, in particular, the immune set point as determined by the basal immune responses. Recent evidence has found that most, if not all, immune response are shaped by the interaction of the immune system with the microbiome[26]. Several experimental models revealed that the efficacy of immune therapies including CpG and checkpoint inhibitors can be influenced by the microbiome.[27] Furthermore, studies in patients on checkpoint inhibitors have shown that the microbiome can predict immune-related toxicity. [28] Thus, for this trial we plan to collect optional fecal samples for microbiome sequencing as a potential biological correlate for efficacy and/or toxicity at baseline, Wk 1, 4, 7, 10 and 13 (up to 1 wk after pembrolizumab). Kits for sample collection will be provided to all participants who opt to participate in this optional part of the trial, upon registration to the trial. Each kit will be provided with a pre-labeled box to be shipped back by the patient for analysis to the laboratory of the Cedars-Sinai Medical Center PI who will be conducting this analysis:

Dr. Stephen Shiao  
Cedars-Sinai Medical Center  
110 N. George Burns Rd #D4094D  
Los Angeles, CA 90048

All specimens will contain the subject's name and date of collection. The shipping and receipt of specimens will be tracked in the Medidata Rave database and by emails sent to the MSK PI and Cedars-Sinai Medical Center PI ([barker@mskcc.org](mailto:barker@mskcc.org); [stephen.shiao@cs.ssi.org](mailto:stephen.shiao@cs.ssi.org)).

### 13.0 CRITERIA FOR REMOVAL FROM STUDY

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons.

A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Confirmed radiographic disease progression  
*Note: A subject may continue on treatment with confirmed radiographic progression if clinically stable or clinically improved.*
- Unacceptable adverse experiences
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- Subject death
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed 24 months of treatment with pembrolizumab

*Note: 24 months of study medication is calculated from the date of first dose.*

*Subjects who stop pembrolizumab after 24 months may be eligible for up to one year of additional study treatment at the discretion of the PI if they responded during the initial 24 months and then progressed after stopping study treatment.*

- Administrative reasons

After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment). Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up, for up to 2 years. After documented disease progression each subject will be followed by telephone for overall survival until death, withdrawal of consent, the end of the study, or 2 years, whichever occurs first.

If consent is withdrawn, the subject will not receive any further investigational product or further study observation.

## **14.0 BIOSTATISTICS**

The primary endpoint of this trial is the overall response rate of non-irradiated lesions in metastatic TNBC treated with RT plus pembrolizumab, as measured by RECIST v 1.1 at Week 13 of the study. A two-stage Simon's optimal design will be employed to test the null hypothesis that the true response rate is  $\leq 5\%$  versus the alternative hypothesis that the true response rate is at least 25%, with type I error rate of 0.05 and type II error rates of 0.20.

In the first stage, we will accrue 9 patients. If no objective tumor responses are observed among these 9 patients, then subject enrollment will be terminated and the study will be declared non-promising. If at least 1 response is observed among these 9 subjects, then the study will be expanded to enroll another 8 patients for a total of 17 treated subjects. At the end of the study, if 2 or fewer objective tumor responses are observed in a cohort, then the study will be considered a failure. If a patient dies before the 13 week assessment, then the death will be considered as a non-response. If at the end of the study  $\geq 3$  tumor responses are observed, then pembrolizumab plus RT will be considered worthwhile. The accrual time is estimated to be 2 years.

### **14.1 Rationale of Null Hypothesis for Primary Endpoint**

As per section 3.1.1, the objective response rates in a single-arm study of pembrolizumab alone in metastatic TNBC patients was 19% by RECIST 1.1, with an additional 25.9% with stable disease (Nanda et al, presented at San Antonio Breast Cancer Symposium 2014). The patients included in this study were all PD-L1 positive, which has been hypothesized to result in higher overall response rates. In our study, we will include both PD-1 positive and PD-1 negative TNBC patients, which may result in lower response rates to pembrolizumab. Furthermore, we anticipate accruing a population of later-line metastatic TNBC patients than were treated in the above study, and that response rates will decline in patients with further lines of therapy. Finally, it is well known that there is currently no "targeted therapy" for TNBC and these patients lack effective therapeutic options. Therefore, we have selected a null hypothesis of 5% as an unacceptable response rate.

## 14.2 Secondary endpoints

For the 1st secondary objective of safety, we will define adverse events as grade 3 toxicities secondary to radiation or grade 4 toxicities of any kind. We will use a sequential stopping rule to assess safety in the following way. If, among the first cohort of 9 patients, we have more than 2 adverse events, then we will stop and declare it unsafe. Or if among the total 17 patients, we have more than 4 adverse events, then we also declare unsafe. The time window for defining an adverse event from treatment will be up to 8 weeks after the completion of RT. This sequential stopping rule for safety has a stopping probability of 0.06 if the true toxicity rate is 10% or lower, and a stopping probability of 0.82 if the true toxicity rate is 35% or higher. Attribution of adverse event due to radiation will be determined by a panel of 3 MSK radiation oncologists.

The secondary objective of overall survival rate will be evaluated by the Kaplan-Meier method. The secondary objective of progression free survival will be evaluated according to RECIST v 1.1 criteria and the Kaplan-Meier method.

The secondary objective of overall response as defined by using the immune-related response criteria (irCR+irPR+irSD) will be evaluated at 13 weeks. This rate will be calculated with a 95% confidence interval. Considering the unique response kinetics that have been observed with immunotherapy, not all new lesions at week 13 may not represent true disease progression. Therefore, for a select proportion of patients who appear to have new lesions on the week 13 scan, a confirmatory scan at week 19 is planned and will be evaluated using the response criteria outline in Section 12.1.1.

## 14.3 Exploratory analyses

Exploratory research studies will be done to evaluate the effect of this therapy on biomarkers using research blood draws, microbiome (fecal) analysis and tumor biopsies at baseline and at week 7( $\pm 1$  wk). Research blood tests will be obtained at baseline and at wks 1, 4, 7, 10 and 13 of pembrolizumab concurrent with routine blood work prior to administration of pembrolizumab. Optional fecal samples will be at baseline and up to 7 days following each cycle of pembrolizumab. Changes from the baseline to post-treatment measures of will be computed as relative proportions. Correlations between these changes and the overall response (as measured by RECIST v. 1.1 or safety will be examined by Wilcoxon rank sum tests.

Association between PDL1 expression with both PFS and ORR will be analyzed using Cox regression and Fisher's exact tests, respectively.

Association between LDH levels at baseline, week 7, and week 13 with both PFS and ORR will be analyzed using Cox regression and Wilcoxon rank sum tests, respectively.

An additional exploratory endpoint will be using PET-Response Criteria (PRC) to assess overall response (CR+PR, for non-targeted, unirradiated lesions) following pembrolizumab + RT. This endpoint will be analyzed descriptively.

## **15.0 PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES**

### **15.1 MSK Research Participant Registration**

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

#### **15.1.1 Registration for Participating Sites**

Central registration for this study will take place through MSK's Clinical Trials Management System (CTMS).

To complete registration and enroll a participant from another institution, the site must first contact the MSK study coordinator to notify him/her of the participant registration.

Once the MSK study coordinator is notified, the site will document the participant's consent by associating the participant to the protocol in CTMS. This will generate a study ID number that is unique and must be written on all data and correspondence for the participant.

After associating the participant to the protocol, the site will enter the consent status in real-time, but no later than 2 business days, from when the informed consent was signed.

The following documents must be saved to CTMS within 2 business days of documenting consent status:

- The completed or partially completed MSK eligibility checklist
- The signed informed consent and HIPAA Authorization form

Supporting source documentation for eligibility questions (e.g. laboratory results, pathology report, radiology reports, MD notes, physical exam sheets, medical history, prior treatment records, and EKG report) will be sent to the MSK study coordinator within 30 days of consent so eligibility can be verified. Once the MSK study coordinator verifies eligibility the site will be notified to enter eligibility and on study status in CTMS, which will complete participant registration.

### **15.2 Randomization**



There is no randomization.

## **16.0 DATA MANAGEMENT ISSUES**

A MSK Research Study Assistant (RSA) from the Department of Radiation Oncology (Breast Service) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinating the activities of the protocol study team.

The data collected for this study will be entered into a secure database (Medidata). Source documentation will be available to support the computerized patient record.

### **16.01 Data and Source Documentation for Participating Sites**

#### **Data**

The participating sites will enter data remotely into electronic Case Report Forms (eCRFs) within the Medidata Rave system. Data entry guidelines have been generated for this study and participating site staff will receive database training prior to enrolling the first participant. The participating site PI is responsible for ensuring these forms are completed accurately and in a timely manner. A Data and Source Documentation Submission Timeline is shown in Table 1 below.

#### **Source Documentation**

Source documentation refers to original records of observations, clinical findings and evaluations that are subsequently recorded as data. Source documentation should be consistent with data entered into eCRFs. Relevant source documentation to be submitted to the MSK study coordinator throughout the study includes:

- Baseline measures to assess pre-protocol disease status (ex. CT, PSA, bone marrow)
- Treatment records
- Toxicities/adverse events that meet study reporting requirements not previously submitted with SAE Reports
- Response designation
- Any other forms of source documentation required per protocol

Source documentation must include a minimum of two identifiers to allow for data verification. MSK will maintain the confidentiality of any subject-identifiable information it may encounter.

**Table 1: Data and Source Documentation Submission Time lines**

<b>Time point</b>	<b>Data</b>	<b>Source Documentation</b>
Baseline	Within 24 hours of consent (see section 15.1.1)	Within 24 hours of consent (see section 15.1.1)

Study Visits	Within 14 days of the study visit	Within 14 days of the study visit
Serious Adverse Events	Within 3 days of event(see section 17.2.1); Updates to be submitted as available	Within 3 days of event (see section 17.2.1)

## 16.1 Quality Assurance

Regular registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action. Random -sample data quality and protocol compliance audits may be conducted by the study team, at a minimum of once per year, more frequently if indicated.

### 16.1.1 Quality Assurance for Participating Sites

#### Monitoring

Each data collection site including MSK will be monitored periodically by MSK. Monitoring visits will be conducted every 4-8 weeks, dependent upon the protocol and patient accrual and activity. The monitor and the participating site will identify a mutually agreeable time for each monitoring visit. At least 10 business days ahead of the visit, the monitor will send the site a notification letter that details the date and expectations of the visit. Monitoring may be conducted remotely or in-person. The monitor must be allowed access to all protocol regulatory and source documents to assess compliance with the protocol, federal regulations and GCPs. The monitor will assess all data for completeness of source documents and to confirm data being recorded in the eCRFs is accurate. If monitoring will be done remotely, sites must agree in advance to provide source documents as required. During onsite visits, the monitor will also inspect and review the facilities and investigational product storage area. The participating site will maintain accurate records of dispensing of study drugs for drug accountability. Drug accountability will be reviewed at monitoring visits. Study drug and bottles must be retained until the monitor performs drug accountability of the study drug(s).

The site Investigator(s) and/or an authorized member of the Investigator's staff should allow sufficient time during monitoring visits to discuss findings. The Investigator(s) or an authorized member of the Investigator's staff will make any necessary corrections during and between monitoring visits

#### Auditing

Each participating site accruing participants to this protocol may be audited by MSK for protocol and regulatory compliance, data verification and source documentation. Audits of selected participant records may be conducted on-site or remotely.

Audits will be summarized and a final report will be sent to the PI at the audited participating site within 30 days of the audit. The report will include a summary of findings, participant-specific case review, recommendations on any performance and/or shortcomings and request for corrective action, when necessary. When corrective action is required, the participating site must reply within 45 days of receipt of the audit report with their corrective action plan.

## **16.2 Data and Safety Monitoring**

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NC I in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials", which can be found at <http://cancertrials.nci.nih.gov/researchers/dsm/index.html>. The DSM Plans at MSK were established and are monitored by the Office of Clinical Research. The MSK DSM Plans can be found on the MSK Intranet at: [http://mskweb5.mskcc.org/intranet/assets/tables/content/359689/Data\\_safety%20Monitoring07.pdf](http://mskweb5.mskcc.org/intranet/assets/tables/content/359689/Data_safety%20Monitoring07.pdf)

## **16.3 Regulatory Documentation**

Prior to implementing this protocol at MSK, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the MSK Institutional Review Board/Privacy Board (IRB/PB). There will be one protocol document and each participating site will utilize that document.

The following documents must be provided to MSK before the participating site can be initiated and begin enrolling participants:

- Participating Site IRB approval(s) for the protocol, appendices, informed consent form and HIPAA authorization
- Participating Site IRB approved informed consent form
- Participating Site 1572
- Conflict of Interest forms for Participating Site Investigators on the 1572
- Participating Site IRB membership list
- Participating Site IRB's Federal Wide Assurance number and OHRP Registration number
- Curriculum vitae and medical license for each investigator and consenting professional
- Documentation of Human Subject Research Certification training for investigators and key staff members at the participating site
- Documentation of Good Clinical Practice (GCP) training for the PI and co-PI at the participating site
- Participating site laboratory certifications and laboratory normal reference ranges

Upon receipt of the required documents, MSK will formally contact the site and grant permission to proceed with enrollment.

### **16.3.1 Amendments**

Each change to the protocol document must be organized and documented by MSK and approved first by the MSK IRB/PB. Protocol amendments that affect MSK only (e.g. change in MSK Co-Investigator, MSK translation, etc.) do not require IRB review at the participating site(s). All other protocol amendments will be immediately distributed to each participating site upon receipt of MSK IRB/PB approval.

Each participating site must obtain IRB approval for all amendments within 45 calendar days of MSK IRB/PB approval. If the amendment is the result of a safety issue or makes eligibility criteria more restrictive, participating sites will not be permitted to continuing enrolling new participants until site IRB approval of the revised protocol documents is granted and submitted to MSK.

#### **Site-Initiated Amendments/Modifications**

Each participating site must provide all site IRB approvals for amendments/modifications and the most current approved version of the site informed consent form and HIPAA authorization at the time of approval. Documents must be submitted to MSK on a continuing basis.

### **16.3.2 Additional IRB Correspondence**

#### Continuing Review Approval

The Continuing Review Approval letter from each participating site's IRB and the most current approved version of the informed consent form must be submitted to MSK within 7 days of expiration. Failure to submit the re-approval in the stated timeline will result in suspension of new participant enrollment.

#### Deviations

A protocol deviation on this study is defined as any incident involving non-adherence to an IRB approved protocol. Deviations typically do not have a significant effect on the rights, safety, or welfare of research participants or on the integrity of the resultant data. Deviations that represent unanticipated problems involving risks to participants or others, or serious adverse events should be reported according to sections 17.3 and 17.5.

Deviations that do not adversely affect the rights and/or welfare of the participant or the scientific validity of the study and are related to protocol scheduling changes outside of the allowed window due to a holiday (e.g., New Year's, Thanksgiving, etc.) and/or inclement weather or other natural event do not require reporting to the MSK IRB/PB. However, they must be clearly documented in the patient's medical record.

#### *Prospective Deviations*

Deviations to the research protocol that involve an informed consent procedure change and/or treatment/pharmacy alterations that are not allowed by the protocol require prospective approval from the MSK IRB/PB prior to the change being carried out. Participating sites should contact the MSK PI who will in turn seek approval from the MSK IRB/PB. Deviations to the research protocol that involve patient eligibility will not be permitted.

#### *Retrospective Deviations*

Deviations that include a change or departure from the research protocol without prior approval from the MSK IRB/PB are considered retrospective deviations. Retrospective deviations should be reported to the MSK PI as soon as possible, who will in turn report the deviation to the MSK IRB/PB as per MSK guidelines.

#### *Participating Site IRB Reporting*

Participating sites should report all deviations to their institution's IRB per local guidelines. Approvals/acknowledgments from the participating site IRB for protocol deviations should be submitted to MSK upon receipt.

#### Other correspondence

Participating sites should submit all other correspondence to their institution's IRB according to local guidelines, and submit copies of official site IRB correspondence, including approvals and acknowledgements, to MSK.

### **16.3.3 Document maintenance**

The MSK PI and participating site PI will maintain adequate and accurate records to fully document protocol implementation and allow data to be subsequently verified.

The participating sites will ensure that all regulatory documents and participating site IRB correspondence are maintained in an on-site regulatory binder and sent to MSK as outlined within the protocol. The on-site regulatory binder will be reviewed by the designated study monitor at monitoring visits. A regulatory binder for each participating site will also be maintained at MSK within the institution's Protocol Information Management System (PIMS).

After study closure, the participating sites will maintain all source documents, study related documents and eCRFs for 7 years.

### **16.4 Noncompliance**

If a participating site is noncompliant with the protocol document, accrual privileges may be suspended and/or contract payments may be withheld, until the outstanding issues have been resolved.

## **17.0 PROTECTION OF HUMAN SUBJECTS**

Participation in this trial is voluntary. All patients will be required to sign a statement of informed consent, which must conform to IRB guidelines.

**Inclusion of Women and Minorities:** Memorial Sloan-Kettering Cancer Center has filed forms HHS 441 (civil rights), HHS (handicapped individual), 639-A (sex discrimination), and 680 (age discrimination); we also take due notice of the NIH policy concerning inclusion of women and minorities in clinical research populations. Patients of all races will be accepted into the protocol. The proposed study population is as described in section 7.0.

**Exclusion of Lactating or Pregnant Women:** Children have been excluded from this study. Triple negative breast cancer is an adult cancer. Thus, the relevance of this drug to the pediatric population has not been established. Lactating and pregnant women are also excluded because of potential anti-proliferative effects of chemotherapy that may be harmful to the developing fetus or nursing infant.

**Benefits:** It is possible that this treatment will result in shrinkage of triple negative breast cancer or in a stabilization of an otherwise progressing disease. It is not known, of course, whether these or any other favorable events will occur. It is not known whether this treatment will affect the overall survival of the patients.

**Costs:** The patient will be responsible for the costs of standard medical care, including, CT scans, all drug administration fees and all hospitalizations, even for complications of treatment. Pembrolizumab will be supplied to patients by Merck at no cost. Patients will not be responsible for the costs of blood procurement obtained for research purposes or the cost for obtaining the tumor biopsy for research purposes.

**Incentives:** No incentives will be offered to patients/subjects for participation in the study.

**Alternatives:** Patients may be eligible for other investigational studies, or focus on palliative care options.

**Confidentiality:** Every effort will be made to maintain patient confidentiality. Research and hospital records are confidential. Patient's name or any other personally identifying information will not be used in reports or publications resulting from this study. The Food and Drug Administration or other authorized agencies (e.g., qualified monitors) may review patients' records and pathology slides, as required.

## **17.1 Privacy**

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

## **17.2 Serious Adverse Event (SAE) Reporting**

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant signs consent. SAE reporting is required for 30-days after the participant's last investigational treatment or intervention. Any events that occur after the 30-day period and that are at least possibly related to protocol treatment must be reported.

If an SAE requires submission to the IRB office per IRB SOP RR-408 „Reporting of Serious Adverse Events“, the SAE report must be sent to the IRB within 5 calendar days of the event. The IRB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office as follows:

For IND/IDE trials: Reports that include a Grade 5 SAE should be sent to [saegrade5@mskcc.org](mailto:saegrade5@mskcc.org). All other reports should be sent to [saemskind@mskcc.org](mailto:saemskind@mskcc.org).

For all other trials: Reports that include a Grade 5 SAE should be sent to [saegrade5@mskcc.org](mailto:saegrade5@mskcc.org). All other reports should be sent to [sae@mskcc.org](mailto:sae@mskcc.org).

The report should contain the following information:

Fields populated from CRDB:

- Subject's initials
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
  - A explanation of how the AE was handled
  - A description of the subject's condition
  - Indication if the subject remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

The PI's signature and the date it was signed are required on the completed report.

For IND/IDE protocols:

The CRDB SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the SAE staff through the IND Office.

#### **17.2.1 Sponsor Serious Adverse Event (SAE) Reporting**

Any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject from the time the consent is signed through 90 days following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to Merck product, must be reported within 5 calendar days to the MSK Safety Office and within 2 working days to Merck Global Safety.

Non-serious Events of Clinical Interest will be forwarded to Merck Global Safety.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to Merck product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor and to Merck.

**SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-993-1220**

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally investigators will submit a copy of these reports to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215 993-1220) at the time of submission to FDA.



All subjects with serious adverse events must be followed up for outcome.

### Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) (see Appendix C) and must be recorded as such on the Adverse Event case report forms/worksheets and reported within 2 working days to Merck Global Safety. If they are serious adverse events, they must be reported to MSK Safety Office within 5 calendar days. (Attn: Worldwide Product Safety; FAX 215 993-1220)

Events of clinical interest for this trial include:

1. An overdose of Merck product, as defined in Section 11.1.3 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.
2. An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.

**\*\*Note:** These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

3. In the event a subject develops any of the following non-serious AEs that do not result in hospitalization, a detailed narrative of the event should be reported as an ECI within 2 working days to Merck Global Safety:
  - a. Grade  $\geq$  3 diarrhea
  - b. Grade  $\geq$  3 colitis
  - c. Grade  $\geq$  2 pneumonitis
  - d. Grade  $\geq$  3 hypo- or hyperthyroidism

A separate guidance document has been provided entitled "event of Clinical Interest and Immune-Related Adverse Event Guidance Document." This document provides guidance regarding identification, evaluation and management of ECIs and irAEs. Additional ECIs are identified in this guidance document and also need to be reported to the Sponsor within 5 calendar days to the MSK Safety Office (only if the ECI is a serious adverse event) and within 2 working days to Merck Global Safety.

Subjects should be assessed for possible ECIs prior to each dose. Lab results should be evaluated and subjects should be asked for signs and symptoms suggestive of an immune-related event. Subjects who develop an ECI thought to be immune-related should have

additional testing to rule out other etiologic causes. If lab results or symptoms indicate a possible immune-related ECI, then additional testing should be performed to rule out other etiologic causes. If no other cause is found, then it is assumed to be immune-related.

ECIs that occur in any subject from the date of first dose through 90 days following cessation of treatment, or the initiation of a new anticancer therapy, whichever is earlier, whether or not related to the Merck's product, must be reported within 5 calendar days to the MSK Safety Office (only if the ECI is a serious adverse event) and within 2 working days to Merck Global Safety.

### **17.3 SAE Reporting for Participating Sites**

#### Responsibilities of Participating Sites

- Participating sites are responsible for reporting all SAEs to their local IRB per local guidelines. Local IRB SAE approvals/acknowledgments must be sent to MSK upon receipt.
- Participating sites are responsible for submitting the SAE Report Form to MSK within 3 calendar day of learning of the event.
- When a death is unforeseen and indicates participants or others are at increased risk of harm, participating sites should notify the MSK PI as soon as possible but within 24 hours of the time the site becomes aware of the event.

#### **SAE contact information:**

Email: ReidyM@mskcc.org to the attention of 16-032 Research Staff (Clinical Research Coordinator Megan Reidy)

AND

MSK PI Dr. Christopher Barker at: barkerc@mskcc.org

#### Responsibilities of MSK

- MSK Research Staff are responsible for submitting all SAEs to the MSK IRB/PB as specified in 17.2 and Merck.
- The MSK PI is responsible for informing all participating sites about all unexpected SAEs that are either possibly, probably, or definitely related to the study intervention within 15 days of receiving the stamped SAE report from the MSK IRB/PB.
- The MSK PI is responsible for informing all participating sites within 24 hours or on the next business day about a death that is unforeseen and indicates participants or others are at increased risk of harm.

### **17.4 Safety Reports**

MSK must submit outside safety reports to the MSK IRB/PB according to institutional guidelines. All outside safety reports will be made available to the participating sites. Outside safety reports that are reportable to the MSK IRB/PB will be distributed to the participating sites immediately upon receiving a stamped copy from the MSK IRB/PB.

Participating sites will receive a special alert for any outside safety reports that warrant a significant change to the conduct of the study. Outside safety reports that are not reportable to the MSK IRB/PB, will be sent to the participating sites monthly.

Participating sites are responsible for submitting safety reports to their site IRB per their local guidelines. All site IRB approvals/acknowledgments of safety reports must be sent to MSK upon receipt.

### **17.5 Unanticipated Problems**

Unanticipated problems involving risks to participants or others (UPs) are defined as any incident, experience or outcome that meets all of the following criteria:

- Unanticipated (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied; and
- Related or possibly related to participating in the research (possibly related means there is a reasonable probability that the incident, experience or outcome may have been caused by procedures involved in the research); and
- Suggests that the research place participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Participating sites are responsible for reporting all UPs to MSK as soon as possible but within 3 calendar days of learning of the event. UPs that are SAEs should be reported to MSK via SAE Report form as per section 17.3. All other UPs should be reported to MSK in a memo signed by the site PI.

MSK is responsible for submitting UPs to the MSK IRB/PB according to institutional guidelines. In addition, MSK is responsible for notifying participating sites of all non-SAE UPs that may affect the sites.

### **18.0 INFORMED CONSENT PROCEDURES**

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.

2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

## **18.1 INFORMED CONSENT PROCEDURES FOR PARTICIPATING SITES**

The investigators listed on the Consenting Professionals Lists at each participating site may obtain informed consent and care for the participants according to good clinical practice and protocol guidelines.

A note will be placed in the medical record documenting that informed consent was obtained for this study, and that the participant acknowledges the risk of participation.

## **19.0 REFERENCES**

1. Wolff AC, Hammond ME, Hicks DG, Dowsett M, McShane LM, et al. (2013) Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. *J Clin Oncol* 31: 3997-4013.
2. Lips EH, Mulder L, Hannemann J, Laddach N, Vrancken Peeters MT, et al. (2011) Indicators of homologous recombination deficiency in breast cancer and association with response to neoadjuvant chemotherapy. *Ann Oncol* 22: 870-876.
3. Deng L, Liang H, Burnette B, Beckett M, Darga T, et al. (2014) Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice. *J Clin Invest* 124: 687-695.
4. Postow MA, Callahan MK, Barker CA, Yamada Y, Yuan J, et al. (2012) Immunologic correlates of the abscopal effect in a patient with melanoma. *N Engl J Med* 366: 925-931.
5. Gelmon K, Dent R, Mackey JR, Laing K, McLeod D, et al. (2012) Targeting triple-negative breast cancer: optimising therapeutic outcomes. *Ann Oncol* 23: 2223-2234.
6. Loi S, Michiels S, Salgado R, Sirtaine N, Jose V, et al. (2014) Tumor infiltrating lymphocytes are prognostic in triple negative breast cancer and predictive for trastuzumab benefit in early breast cancer: results from the FinHER trial. *Ann Oncol* 25: 1544-1550.
7. Loi S, Sirtaine N, Piette F, Salgado R, Viale G, et al. (2013) Prognostic and predictive value of tumor-infiltrating lymphocytes in a phase III randomized adjuvant breast cancer

- trial in node-positive breast cancer comparing the addition of docetaxel to doxorubicin with doxorubicin-based chemotherapy: BIG 02-98. *J Clin Oncol* 31: 860-867.
8. Denkert C, von Minckwitz G, Brase JC, Sinn BV, Gade S, et al. (2015) Tumor-infiltrating lymphocytes and response to neoadjuvant chemotherapy with or without Carboplatin in human epidermal growth factor receptor 2-positive and triple-negative primary breast cancers. *J Clin Oncol* 33: 983-991.
  9. Adams S, Gray RJ, Demaria S, Goldstein L, Perez EA, et al. (2014) Prognostic value of tumor-infiltrating lymphocytes in triple-negative breast cancers from two phase III randomized adjuvant breast cancer trials: ECOG 2197 and ECOG 1199. *J Clin Oncol* 32: 2959-2966.
  10. Kuo WH, Chang YY, Lai LC, Tsai MH, Hsiao CK, et al. (2012) Molecular characteristics and metastasis predictor genes of triple-negative breast cancer: a clinical study of triple-negative breast carcinomas. *PLoS One* 7: e45831.
  11. Miyashita M, Sasano H, Tamaki K, Chan M, Hirakawa H, et al. (2014) Tumor-infiltrating CD8+ and FOXP3+ lymphocytes in triple-negative breast cancer: its correlation with pathological complete response to neoadjuvant chemotherapy. *Breast Cancer Res Treat* 148: 525-534.
  12. Salgado R, Denkert C, Demaria S, Sirtaine N, Klauschen F, et al. (2014) Harmonization of the evaluation of tumor infiltrating lymphocytes (TILs) in breast cancer: recommendations by an international TILs-working group 2014. *Ann Oncol*.
  13. Topalian SL, Drake CG, Pardoll DM (2012) Targeting the PD-1/B7-H1 (PD-L1) pathway to activate anti-tumor immunity. *Curr Opin Immunol* 24: 207-212.
  14. Emens LA, Braithe FS, Cassier PA, Delord J, Eder JP, et al. Inhibition of PD-L1 by MPDL3280A leads to clinical activity in patients with metastatic triple-negative breast cancer; 2014 December 8-13, 2014; San Antonio, TX
  15. Formenti SC, Demaria S (2009) Systemic effects of local radiotherapy. *Lancet Oncol* 10: 718-726.
  16. Dewan MZ, Galloway AE, Kawashima N, Dewyngaert JK, Babb JS, et al. (2009) Fractionated but not single-dose radiotherapy induces an immune-mediated abscopal effect when combined with anti-CTLA-4 antibody. *Clin Cancer Res* 15: 5379-5388.
  17. Demaria S, Kawashima N, Yang AM, Devitt ML, Babb JS, et al. (2005) Immune-mediated inhibition of metastases after treatment with local radiation and CTLA-4 blockade in a mouse model of breast cancer. *Clin Cancer Res* 11: 728-734.
  18. Kachikwu EL, Wamoto KS, Liao YP, DeMarco JJ, Agazaryan N, et al. (2011) Radiation enhances regulatory T cell representation. *Int J Radiat Oncol Biol Phys* 81: 1128-1135.
  19. Jobling MF, Mott JD, Finnegan MT, Jurukovski V, Erickson AC, et al. (2006) Isoform-specific activation of latent transforming growth factor beta (LTGF-beta) by reactive oxygen species. *Radiat Res* 166: 839-848.
  20. Verbrugge I, Hagekyriakou J, Sharp LL, Galli M, West A, et al. (2012) Radiotherapy increases the permissiveness of established mammary tumors to rejection by immunomodulatory antibodies. *Cancer Res* 72: 3163-3174.
  21. Formenti SC, Demaria S (2013) Combining radiotherapy and cancer immunotherapy: a paradigm shift. *J Natl Cancer Inst* 105: 256-265.
  22. Lugade AA, Moran JP, Gerber SA, Rose RC, Frelinger JG, et al. (2005) Local radiation therapy of B16 melanoma tumors increases the generation of tumor antigen-specific effector cells that traffic to the tumor. *J Immunol* 174: 7516-7523.
  23. Wahl RL, Jacene H, Kasamon Y, Lodge MA (2009) From RECIST to PERCIST: Evolving Considerations for PET response criteria in solid tumors. *J Nucl Med* 50 Suppl 1: 122S-150S.
  24. Lesokhin AM, Hohl TM, Kitano S, Cortez C, Hirschhorn-Cymerman D, et al. (2012) Monocytic CCR2(+) myeloid-derived suppressor cells promote immune escape by limiting activated CD8 T-cell infiltration into the tumor microenvironment. *Cancer Res* 72: 876-886.

25. Hooper LV, Littman DR, Macpherson AJ (2012) Interactions between the microbiota and the immune system. *Science* 336: 1268-1273.
26. Iida N, Dzutsev A, Stewart CA, Smith L, Bouladoux N, et al. (2013) Commensal bacteria control cancer response to therapy by modulating the tumor microenvironment. *Science* 342: 967-970.
27. Sivan A, Corrales L, Hubert N, Williams JB, Aquino-Michaels K, et al. (2015) Commensal *Bifidobacterium* promotes antitumor immunity and facilitates anti-PD-L1 efficacy. *Science* 350: 1084-1089.

## **20.0 APPENDICES**

APPENDIX B: Requisition for Research Biopsy Specimens

APPENDIX C: PEMBROLIZUMAB PROGRAM (MK-3475) Event of Clinical Interest  
Guidance Document, Version 5.0

APPENDIX D: MK-3475 Drug Preparation Instructions" manual